Devi, S.
09/921157

- key terms

FILE 'REGISTRY' ENTERED AT 12:25:55 ON 04 SEP 2002
E CYTOTOXIN/CN
L1 7 S E15-E23

FILE 'HCAPLUS' ENTERED AT 12:26:35 ON 04 SEP 2002
L1 7 SEA FILE=REGISTRY ABB=ON PLU=ON ("CYTOTOXIN (HELICOBACTER PYLORI CLONE TOXEE1 PRECURSOR)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI GENE VACA FRAGMENT)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI GENE VACA PRECURSOR)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI PRECURSOR REDUCED)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI PRECURSOR)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI STRAIN 26695 VACUOLATING OPEN READING FRAME HP0887)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI STRAIN 87-203 GENE VACA FRAGMENT REDUCED)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI TYPE I GENE VACA)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI)"/CN)
L2 383 SEA FILE=HCAPLUS ABB=ON PLU=ON (L1 OR CT OR CYTOTOXIN OR CYTO TOXIN) AND VACUOL?
L3 19 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 AND RECOMBINAN?

L4 225 SEA FILE=HCAPLUS ABB=ON PLU=ON (VAC A OR VACA)(S)(CT OR CYTOTOXIN OR CYTO TOXIN)
L5 225 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 AND (HP OR PYLORI)
L6 13 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 AND RECOMBINAN?

L7 20 L3 OR L6

L7 ANSWER 1 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:689464 HCAPLUS
DOCUMENT NUMBER: 135:342196
TITLE: VacA pores as portable portals for urea
AUTHOR(S): Merchant, Juanita L.
CORPORATE SOURCE: Internal Medicine and Physiology, University of Michigan, Ann Arbor, MI, 48109-0650, USA
SOURCE: Journal of Clinical Investigation (2001), 108(6), 803-804
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with refs., discussing VacA, a toxin expressed by most clin. isolates of Helicobacter pyrola, as portable portals for urea. H. pyrola thrives at low pH, according to Warren and Marshall, and is known to be the major mechanism by which ulcers of the upper gastrointestinal tract are induced. Coincubation of **recombinant** VacA protein with gastric cell lines induces **vacuole** formation in the cytoplasm, and VacA-expressing strains seems to colonize the stomach more efficiently. H. **pylori** VacA binds preferentially to the apical plasma membrane, permeabilizing the host cell to urea. In vitro studies demonstrate that VacA protein is not required to induce an inflammatory response and colonize animal models, indicating that non-VacA H. **pylori** strains must be able to transport urea effectively to survive in the acidic stomach.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE

FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:650920 HCAPLUS
DOCUMENT NUMBER: 135:206779
TITLE: Two Distinctive Cell Binding Patterns by **Vacuolating** Toxin Fused with Glutathione S-Transferase: One High-Affinity m1-Specific Binding and the Other Lower-Affinity Binding for Variant m Forms
AUTHOR(S): Wang, Wen-Ching; Wang, Hung-Jung; Kuo, Chun-Hsien
CORPORATE SOURCE: Department of Life Science, National Tsing Hua University, Hsinchu, Taiwan
SOURCE: Biochemistry (2001), 40(39), 11887-11896
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Helicobacter pylori VacA causes large intracellular **vacuoles** in epithelial cells such as HeLa or RK13 cells. Two major VacA forms, m1 and m2, divergent in an .apprx.300 amino acid segment within the cell binding domain P58, display distinct cell-type specificity. Sequence anal. of four vacA alleles showed that a m1-like allele (61) and two m2 alleles (62 and v226) mainly differed in the midregion and that v225, a m1m2 chimera, was a natural double crossover from v226 and another allele. Each of these alleles was expressed as a sol. GST-VacA fusion that did not form a large oligomer. The **recombinant** VacA portion nevertheless assembled into higher ordered structures and possessed biol. binding activity similar to that of the native VacA. A direct comparison of fusion-cell binding activity showed that m1 > m1m2 > m2 in HeLa cells, whereas there were more similar activities in RK13 cells. **Vacuolating** analyses of three forms revealed a pos. correlation between cell binding activity and **vacuolating** activity. Moreover, the m1-type N-terminal half portion of the midregion was crucial for HeLa cell cytotoxicity. Kinetic, Scatchard, and inhibition analyses suggested the presence of at least two receptors: a m1-type specific high-affinity receptor (Kd = 5 nM) and a common VacA receptor interacting similarly with m1, m1m2, and m2 via a lower affinity (Kd = 45-67 nM). Expression of mainly the m1-type receptor on HeLa cells whereas both receptors on RK13 cells may account for distinct cell binding activity and therefore for cell-type specificity.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:553801 HCAPLUS
DOCUMENT NUMBER: 136:273770
TITLE: Construction and expression of prokaryotic expression vector of Helicobacter **pylori** (**Hp**) vac A gene related segment with **vacuolating** activity
AUTHOR(S): Jiang, Hong; Yan, Xiaojun; Su, Chengzhi; Han, Fengchan; Feng, Yongqiang; Hou, Yu

CORPORATE SOURCE: Institute of Gene Diagnosis, Fourth Military Medical University, Xi'an, 710032, Peop. Rep. China
SOURCE: Xibao Yu Fenzi Mianyixue Zazhi (2001), 17(3), 237-240
CODEN: XFMZFM; ISSN: 1007-8738
PUBLISHER: Disi Junyi Daxue
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The prokaryotic expression vector carrying a fragment of Helicobacter **pylori** (**Hp**) **vacuolating cytotoxin** A (**vac A**) gene was constructed and it was expressed in E.coli. Using PCR and **recombinant** DNA techniques, the segment B of **Hp** vac A gene was amplified, cloned into clone vector pGEM-3Zf(-), sequenced and then cloned into expression vector pRSETA. Thus the prokaryotic expression vector of a segment related with **vacuolating** activity of **Hp** vac A gene was constructed. After induction with 5 x 103 mM IPTG for 4h, a fusion protein with relative mol. mass of 33,000 was expressed, representing 47.8% of total bacterial protein in E.coli. The fusion protein in lysate supernatant amounted to 10.9% of total bacterial protein. It was showed that the protein could be bound to rabbit anti-Vac A antibody by ELISA and Western blot anal. The prokaryotic expression vector was constructed successfully, so that provided an expt. basis for analyzing the biol. function of this segment and predicting **Hp** infection by virtue of detecting the patient's sera.

L7 ANSWER 4 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:549226 HCAPLUS
DOCUMENT NUMBER: 135:176587
TITLE: **Vacuolating cytotoxin** of Helicobacter **pylori** induces apoptosis in the human gastric epithelial cell line AGS
AUTHOR(S): Kuck, Dirk; Kolmerer, Bernhard; Iking-Konert, Christof; Krammer, Peter H.; Stremmel, Wolfgang; Rudi, Jochen
CORPORATE SOURCE: Department of Medicine, University of Heidelberg, Heidelberg, 69115, Germany
SOURCE: Infection and Immunity (2001), 69(8), 5080-5087
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Helicobacter **pylori** induces cell death by apoptosis. However, the apoptosis-inducing factor is still unknown. The virulence factor **vacuolating cytotoxin** A (**VacA**) is a potential candidate, and thus its role in apoptosis induction was investigated in the human gastric epithelial cell line AGS. The supernatant from the vacA wild-type strain P12 was able to induce apoptotic cell death, whereas the supernatant from its isogenic mutant strain P14 could not. That VacA was indeed the apoptosis-inducing factor was demonstrated further by substantial redn. of apoptosis upon treatment of AGS cells with a supernatant specifically depleted of native VacA. Furthermore, a **recombinant** VacA produced in Escherichia coli was also able to induce apoptosis in AGS cells but failed to induce cellular **vacuolation**. These findings demonstrate that the

vacuolating cytotoxin of H. **pylori** is a bacterial factor capable of inducing apoptosis in gastric epithelial cells.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:470952 HCAPLUS
DOCUMENT NUMBER: 136:145883
TITLE: Population genetics of Helicobacter **pylori** in the southern part of Switzerland analysed by sequencing of four housekeeping genes (atpD, glnA, scoB and recA), and by vacA, cagA, iceA and IS605 genotyping
AUTHOR(S): Maggi Solca, Nadia; Bernasconi, Marco V.; Valsangiacomo, Claudio; Van Doorn, Leen-Jan; Piffaretti, Jean-Claude
CORPORATE SOURCE: Istituto Cantonale Batteriosierologico, Lugano, 6904, Switz.
SOURCE: Microbiology (Reading, United Kingdom) (2001), 147(6), 1693-1707
CODEN: MROBEO; ISSN: 1350-0872
PUBLISHER: Society for General Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The population biol. of 78 H. **pylori** strains (71 from Swiss Italian, 4 from East Asian and 3 from South African patients) was investigated by sequence anal. of 4 housekeeping genes: atpD, scoB, glaA and recA. The vacA genotype, the presence of cagA and IS605, the iceA allelic type, and the resistance to metronidazole, clarithromycin and amoxycillin were detd. A high percentage of DNA polymorphic sites (19.8% for atpD, 21.3% for scoB, 23.7% for glnA and 20.3% for recA) was found. The phylogenetic trees based on the nucleotide sequences of the 4 gene fragments showed different topologies and were incongruent. The virulence-assocd. markers were distributed over the dendrograms and no assocn. was found with phylogenetic clusters or clin. manifestations (chronic gastritis, gastric or duodenal ulcer, MALT lymphoma). Moreover, the H ratios (calcd. with the homoplasy test) ranged from 0.742 to 0.799, depending on the gene fragment examd. All these observations suggest that H. **pylori** exists as a **recombinant** population. The clustering of the strains according to their geog. origin (USA/Europe, East Asia, South Africa) that has recently been demonstrated elsewhere could only be confirmed for the East Asian vacA s1c strains. In contrast, the South African strains clustered together only in the atpD tree. Presumably, recombination at the different loci has masked the evolutionary relationship among the strains.
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:341378 HCAPLUS
DOCUMENT NUMBER: 135:2593
TITLE: Virulence factors of Helicobacter pylori
AUTHOR(S): Dundon, William G.; De Bernard, Marina;

Montecucco, Cesare
CORPORATE SOURCE: Centro CNR Biomembrane and Dipartimento di Scienze Biomediche, Universita di Padova, Padua, I-35121, Italy
SOURCE: International Journal of Medical Microbiology (2001), 290(8), 647-658
CODEN: IMEMFV; ISSN: 1438-4221
PUBLISHER: Urban & Fischer Verlag
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with many refs. A no. of virulence factors were identified and characterized from the gastric pathogen Helicobacter pylori. The **vacuolating** toxin (VacA) is a major determinant of H. pylori-assocd. gastric disease. In non-polarized cells, VacA alters the endocytic pathway, resulting in the release of acid hydrolases and the redn. of both extracellular ligand degrdn. and antigen processing. The toxin forms trans-membrane anion-specific channels and reduces the transepithelial elec. resistance of polarized monolayers. Localization of the VacA channels in acidic intracellular compartments causes osmotic swelling which, together with membrane fusion, leads to **vacuole** formation. The neutrophil-activating protein of H. pylori (HP-NAP) induces the prodn. of O radicals in human neutrophils via a cascade of intracellular activation events which may contribute to the damage of the stomach mucosa. This protein was recently shown to be an important antigen in the human immune response to H. pylori infection. In addn., mice vaccinated with **recombinant** HP-NAP were protected against H. pylori challenge. H. pylori strains that are assocd. with severe tissue damage and inflammation possess the Cag pathogenicity island that contains several genes encoding factors involved in the induction of proinflammatory cytokines/chemokines and of a type IV secretion system involved in the delivery of a highly immunogenic protein, CagA, into eukaryotic cells. Recent advances in our understanding of the involvement of VacA, HP-NAP, and the CagA/Type IV secretion system in the H. pylori-assocd. disease process are discussed in this review.
REFERENCE COUNT: 111 THERE ARE 111 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:330653 HCAPLUS
DOCUMENT NUMBER: 135:356508
TITLE: Assessment of Helicobacter **pylori** vacA and cagA genotypes and host serological response
AUTHOR(S): Figueiredo, Ceu; Quint, Wim; Nouhan, Nathalie; Van Den Munckhof, Henk; Herbrink, Paul; Scherpenisse, Joost; De Boer, Wink; Schneeberger, Peter; Perez-Perez, Guillermo; Blaser, Martin J.; Van Doorn, Leen-Jan
CORPORATE SOURCE: Delft Diagnostic Laboratory, Delft, 2625 AD, Neth.
SOURCE: Journal of Clinical Microbiology (2001), 39(4), 1339-1344
CODEN: JCMIDW; ISSN: 0095-1137
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Helicobacter **pylori** strains can be distinguished by genotyping of virulence-assocd. genes, such as vacA and cagA. Because serol. discrimination between strain types would reduce the need for endoscopy, 61 patients carrying H. **pylori** were studied by vacA and cagA genotyping of H. **pylori** in gastric biopsy specimens and by detection of specific serum antibodies. Serol. responses to H. **pylori** were detd. by Helicoblot (versions 2.0 and 2.1). Antibodies to CagA also were detd. by a rapid anti-CagA assay (Pyloriset screen CagA) as well as by two noncommercially developed enzyme immunoassays, each using a **recombinant** CagA protein. Assessment of performance of the Helicoblot assays indicated substantial interobserver variation, with kappa values between 0.20 and 0.93. There was no relationship between the serol. profiles on the Helicoblot and the genotypes from the same patients, except for strong assocns. between the presence of anti-CagA and the cagA-pos. and vacA s1 H. **pylori** genotypes. Detection of anti-CagA by the five different assays varied considerably, with kappa values ranging from 0.21 to 0.78. Using the cagA genotype as the "gold std.," the sensitivity and specificity of the anti-CagA assays varied from 71.4 to 85.7% and from 54.2 to 100%, resp. Thus, serol. profiles of antibodies to H. **pylori** are heterogeneous and, with the exception of anti-CagA antibodies, show no relation to the H. **pylori** vacA and cagA genotypes. Detection of anti-CagA antibodies is strongly dependent on the test used.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 20 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:207374 HCAPLUS

DOCUMENT NUMBER: 134:362546

TITLE: Helicobacter **pylori** **vacuolating cytotoxin** binding to a putative cell surface receptor, heparan sulfate, studied by surface plasmon resonance

AUTHOR(S): Utt, M.; Danielsson, B.; Wadstrom, T.

CORPORATE SOURCE: Deoartment of Infectious Diseases and Medical Microbiology, Lund University, Lund, S-223 62, Swed.

SOURCE: FEMS Immunology and Medical Microbiology (2001), 30(2), 109-113
CODEN: FIMIEV; ISSN: 0928-8244

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The H. **pylori** **vacuolating cytotoxin** or **VacA** toxin is a major virulence factor in H. **pylori** infection and type B gastritis. The authors predicted heparin/heparan sulfate (H/HS) binding properties of the 58-kDa subunit of **VacA cytotoxin** using bioinformatics tools and showed this by surface plasmon resonance (SPR)-based biosensor studies. Putative H/HS binding peptides were synthesized and binding to HS was shown by SPR in the absence or presence of trifluoroethanol. The authors found that a **recombinant** **cytotoxin VacA** polypeptide binds to surface-immobilized HS and propose that HS might be a receptor/co-receptor for H. **pylori** **VacA**

cytotoxin.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:221320 HCAPLUS
DOCUMENT NUMBER: 133:29416
TITLE: Comparison of serum antibody titers to Helicobacter pylori lipopolysaccharides, CagA, VacA and partially purified cellular extracts in a Japanese population
AUTHOR(S): Yokota, S.-i.; Amano, K.-i.; Fujii, N.; Yokochi, T.
CORPORATE SOURCE: Hondo, 1-1-1, Central Research Laboratory, Akita University School of Medicine, Akita, Japan
SOURCE: FEMS Microbiology Letters (2000), 185(2), 193-198
CODEN: FMLED7; ISSN: 0378-1097
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors examd. the levels of antibody titers against Helicobacter pylori antigens, three types of lipopolysaccharides (LPSs), **recombinant** CagA antigen, **recombinant** VacA antigen and partially purified cellular antigens in the sera of Japanese volunteers. The three types of LPSs are LPS carrying the highly antigenic epitope, LPS carrying the weakly antigenic epitope and rough LPS, classified on the basis of antigenicity in humans. IgG titers against all H. pylori antigens tested were significantly different between gastroduodenal patients and healthy adults without H. pylori infection. IgG titers against LPS carrying the weakly antigenic epitope, rough LPS and VacA antigen, as well as IgA titers against the partially purified cellular ext. were significantly higher in gastroduodenal patients than in H. pylori-pos. healthy adults. However, IgG titers against LPS carrying the highly antigenic epitope, CagA antigen or the partially purified cellular ext. showed no significant difference between patients and H. pylori-pos. healthy adults. The results indicated that increases in IgG titers against VacA antigen and the weakly antigenic and core epitopes of LPS, and in IgA titer against the partially purified cellular ext., were assocd. with disease state and may be useful in identifying active infection of H. pylori.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:52931 HCAPLUS
DOCUMENT NUMBER: 133:16046
TITLE: Serological response to Helicobacter **pylori recombinant** antigens in Chilean infected patients with duodenal ulcer, non-ulcer dyspepsia and gastric cancer
AUTHOR(S): Opazo, Patricio; Muller, Ilse; Rollan, Antonio; Valenzuela, Pablo; Yudelevich, Arturo; Garcia-De La Guarda, Ruth; Urra, Soledad; Venegas, Alejandro

CORPORATE SOURCE: Unidad de Biologia Molecular, Unidad de Biologia Molecular, BIOS Chile IGSA, Santiago, Chile
SOURCE: APMIS (1999), 107(12), 1069-1078
CODEN: APMSEL; ISSN: 0903-4641
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have previously cloned 10 Helicobacter **pylori** antigen genes from a Chilean strain including: **cytotoxin VacA**, a truncated region of CagA (called A17), a species-specific protein (Ag26), urease subunits (UreA, UreB), a flagellin, (FlaB), heat shock proteins (HspA and HspB), an adhesin (HpaA) and a lipoprotein (Lpp20). Immunogenicity of these antigens was tested by immunoblot with sera of Chilean infected patients, revealing that HpaA, A17, HspB and VacA were more frequently recognized (86%, 82%, 68% and 68%, resp.). According to the clin. condition, it was detd. that Lpp20 was preferentially recognized by sera from non-ulcer dyspepsia patients (80%), A17 and VacA by patients with duodenal ulcer (92% and 83% resp.), and HspB by patients with duodenal ulcer (83%) and gastric cancer (90%). An ELISA was developed with a purified mixt. of A17 and VacA antigens to test the different groups of patients. It was found that sera from duodenal ulcer patients showed higher values than those from non-ulcer dyspepsia patients, but this difference was not significant. Moreover, sera from gastric cancer patients showed values lower than those from non-ulcer dyspepsia patients. These results indicate that, in the Chilean population, antibodies raised against VacA and A17 are not markers either for duodenal ulcer or for gastric cancer.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:796842 HCAPLUS
DOCUMENT NUMBER: 132:147346
TITLE: A plasmid-based vector system for the cloning and expression of Helicobacter **pylori** genes encoding outer membrane proteins
AUTHOR(S): Fischer, W.; Schwan, D.; Gerland, E.; Erlenfeld, G. E.; Odenbreit, S.; Haas, R.
CORPORATE SOURCE: Max von Pettenkofer-Institut fur Hygiene und Medizinische Mikrobiologie, Ludwig-Maximilians-Universitat, Munchen, D-80336, Germany
SOURCE: Molecular and General Genetics (1999), 262(3), 501-507
CODEN: MGGEAE; ISSN: 0026-8925
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Helicobacter **pylori** produces a no. of proteins assocd. with the outer membrane, including adhesins and the **vacuolating cytotoxin**. We obsd. that the functional expression of such proteins is deleterious to Escherichia coli, the host bacterium used for gene cloning. Therefore, a general method was developed for the functional expression of such genes on a shuttle vector in H. **pylori**, which has been termed SOMPES (Shuttle vector-based Outer Membrane Protein

Expression System). The intact, active gene is reconstituted by recombination in H. **pylori** from partial gene sequences cloned on a E. coli-H. **pylori** shuttle vector. This system was established in an H. **pylori** strain carrying a precise, unmarked chromosomal deletion of the vacA gene, which was constructed by adapting the streptomycin sensitivity system to H. **pylori**. It is based on the expression of the H. **pylori** rpsL gene as a counter-selectable marker in the genetic background of an rpsL mutant. The utility of this approach is demonstrated by the expression of a **recombinant** gene encoding **vacuolating cytotoxin (vacA)** and a **recombinant** gene encoding an adherence-assocd. outer membrane protein (alpA) in H. **pylori**.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 12 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:529264 HCAPLUS
DOCUMENT NUMBER: 131:169280
TITLE: Antigen library immunization
INVENTOR(S): Punnonen, Juha; Bass, Steven H.; Whalen, Robert Gerald; Howard, Russell; Stemmer, Willem P. C.
PATENT ASSIGNEE(S): Maxygen, Inc., USA
SOURCE: PCT Int. Appl., 153 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9941383	A1	19990819	WO 1999-US2944	19990210
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2320958	AA	19990819	CA 1999-2320958	19990210
AU 9932891	A1	19990830	AU 1999-32891	19990210
EP 1054973	A1	20001129	EP 1999-932510	19990210
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 2001006950	A1	20010705	US 1999-247888	19990210
JP 2002507393	T2	20020312	JP 2000-531564	19990210

PRIORITY APPLN. INFO.:

US 1998-21769	A	19980211
US 1998-74294P	P	19980211
US 1998-105509P	P	19981023
WO 1999-US2944	W	19990210

AB This invention is directed to antigen library immunization, which provides methods for obtaining **recombinant** multivalent antigens having improved properties for therapeutic and other uses. The methods are useful for obtaining improved antigens that can

induce an immune response against pathogens, cancer, and other conditions, as well as antigens that are effective in modulating allergy, inflammatory and autoimmune diseases.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 13 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:717312 HCAPLUS
DOCUMENT NUMBER: 130:108808
TITLE: Comparison of four serological tests to determine the CagA or VacA status of Helicobacter **pylori** strains
AUTHOR(S): Yamaoka, Yoshio; Kodama, Tadashi; Graham, David Y.; Kashima, Kei
CORPORATE SOURCE: Department of Medicine, Veterans Affairs Medical Center and Baylor College of Medicine, Houston, TX, 77030, USA
SOURCE: Journal of Clinical Microbiology (1998), 36(11), 3433-3434
CODEN: JCMIDW; ISSN: 0095-1137
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We compared four tests for antibodies to CagA or VacA, HelicoBlot 2.0, RIDA Blot Helicobacter, CHIRON RIBA H. **pylori** SIA, and an ELISA using **recombinant** CagA. Immunoblot assays were accurate for detg. Helicobacter **pylori** status but poor for detg. CagA or VacA status (accuracy, 66 to 80% for CagA status and 34 to 67% for VacA status). None can be recommended for detg. CagA or VacA status.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 14 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:419489 HCAPLUS
DOCUMENT NUMBER: 129:187685
TITLE: The inhibition of cell proliferation by Helicobacter pylori products
AUTHOR(S): Chmiela, M.; Covacci, A.; Waldstrom, T.; Rudnicka, W.
CORPORATE SOURCE: Department of Infectious Biology, University of Lodz, Lodz, Pol.
SOURCE: Zentralblatt fuer Bakteriologie, Supplement (1997), 29(Bacterial Protein Toxins), 214-215
CODEN: ZBASE2; ISSN: 0941-018X
PUBLISHER: Gustav Fischer Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB H. pylori infections progress in spite of specific immune response. This suggests that bacterial factors may inhibit the protective immunol. reactions of the host. Previously it was shown that somatic fraction of H. pylori inhibited the response of T cells to PHA. Bacterial LPS as a possible cause of the inhibitory effect was excluded. Somatic fractions for the strains differing by **vacuolating cytotoxin** activity demonstrated similar inhibitory effect towards T cells. The CagA protein was

considered by the authors as one of bacterial agents which could be responsible partly for the paralyzing effect of bacterial somatic fractions. In the present study, **recombinant** CagA inhibited the PHA-induced response of T cells but also proliferation of THP-1 monocytes grown in the medium with GM-CSF. The inhibition of cell functions by H. pylori products may prevent the development of antimicrobial cellular immunity.

L7 ANSWER 15 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:238853 HCAPLUS
DOCUMENT NUMBER: 128:306033
TITLE: Major virulence factors, VacA and CagA, are commonly positive in Helicobacter **pylori** isolates in Japan
AUTHOR(S): Maeda, S.; Ogura, K.; Yoshida, H.; Kanai, F.; Ikenoue, T.; Kato, N.; Shiratori, Y.; Omata, M.
CORPORATE SOURCE: Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo, 113, Japan
SOURCE: Gut (1998), 42(3), 338-343
CODEN: GUTTAK; ISSN: 0017-5749
PUBLISHER: BMJ Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB VacA and CagA proteins have been reported to be major virulence factors of Helicobacter **pylori**. However, antibodies against these proteins are frequently found in the sera of Japanese patients regardless of their gastroduodenal status. To evaluate the expression of VacA and CagA proteins by H **pylori** strains isolated in Japan. By using specific antibodies raised against **recombinant** VacA and CagA proteins, the expression of VacA and CagA was evaluated in 68 H **pylori** strains isolated from Japanese patients; a **vacuolating** assay and genotyping of the vacA gene were also used in the evaluation. The results were analyzed in relation to the gastroduodenal diseases of the hosts. VacA and CagA proteins were expressed in 59/68 (87%) and in 61/68 (90%) isolates resp. The **vacuolating** assay was pos. in 57/68 (84%) isolates, indicating that most immunol. **VacA** pos. strains produced active **cytotoxin**. The prevalence of infection with strains expressing CagA and pos. for **vacuolating** activity (Type I) was very high, 54/68 (79%), irresp. of the gastroduodenal status of the host. Most H. **pylori** isolates in Japan are pos. for **vacuolating** **cytotoxin** and CagA, and thus these virulence factors cannot be used as markers to discern the risk of developing serious gastroduodenal pathologies in the hosts. However, the high prevalence of infection with strains pos. for **vacuolating** **cytotoxin** and CagA may contribute to the characteristics of H **pylori** infection in Japan.

L7 ANSWER 16 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:773428 HCAPLUS
DOCUMENT NUMBER: 128:60458
TITLE: Therapeutic intragastric vaccination against Helicobacter **pylori** in mice eradicates an otherwise chronic infection and confers protection against reinfection
AUTHOR(S): Ghiara, Paolo; Rossi, Michela; Marchetti, Marta;

Di Tommaso, Annalisa; Vindigni, Carla; Ciampolini, Fabrizio; Covacci, Antonello; Telford, John L.; De Magistris, Maria Teresa; Pizza, Mariagrazia; Rappuoli, Rino; Del Giudice, Giuseppe
CORPORATE SOURCE: IRIS, Chiron Vaccines Immunobiological Research Institute Siena, University of Siena, Siena, 53100, Italy
SOURCE: Infection and Immunity (1997), 65(12), 4996-5002
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Chronic infection of the gastroduodenal mucosae by the gram-neg. spiral bacterium Helicobacter **pylori** is responsible for chronic active gastritis, peptic ulcers, and gastric cancers such as adenocarcinoma and low-grade gastric B-cell lymphoma. The success of eradication by antibiotic therapy is being rapidly hampered by the increasing occurrence of antibiotic-resistant strains. An attractive alternative approach to combat this infection is represented by the therapeutic use of vaccines. In the present work, we have exploited the mouse model of persistent infection by mouse-adapted H. **pylori** strains that we have developed to assess the feasibility of the therapeutic use of vaccines against infection. We report that an otherwise chronic H. **pylori** infection in mice can be successfully eradicated by intragastric vaccination with H. **pylori** antigens such as **recombinant** VacA and CagA, which were administered together with a genetically detoxified mutant of the heat-labile enterotoxin of Escherichia coli (referred to as LTK63), in which the serine in position 63 was replaced by a lysine. Moreover, we show that therapeutic vaccination confers efficacious protection against reinfection. These results represent strong evidence of the feasibility of therapeutic use of VacA- or CagA-based vaccine formulations against H. **pylori** infection in an animal model and give substantial preclin. support to the application of this kind of approach in human clin. trials.

L7 ANSWER 17 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:641643 HCAPLUS
DOCUMENT NUMBER: 125:325670
TITLE: Immunogenicity of purified and **recombinant** antigens of Helicobacter **pylori** in the mouse
AUTHOR(S): Odera, G.; Burroni, D.; Bugnoli, M.; Ghiara, P.
CORPORATE SOURCE: Biocine SpA, Siena, 53100, Italy
SOURCE: Mikrooekologie und Therapie (1995), 25(Beitraege zum XIX. Internationalen Kongress fuer Mikrobielle Oekologie und Krankheiten, 1994), 139-143
CODEN: MITHE4; ISSN: 0720-0536
PUBLISHER: Institut fuer Mikrooekologie
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mice were orally and peranterally immunized with 94 kDa **cytotoxin** (**VacA**) and urease from H. **pylori** . Both VacA and urease were highly immunogenic when injected parenterally. Serum IgG to urease A and urease B were present in

mice immunized with purified urease s.c. Neither antigen induced an antibody response when administered orally. Neither oral or parenteral immunization protected from gastric damage after oral challenge with cytotoxin-producing H. **pylori**. Oral immunization with ureas plus heat-labile enterotoxin prevented H. **pylori** colonization after oral challenge with a suspension of H. **pylori**.

L7 ANSWER 18 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:606409 HCAPLUS
DOCUMENT NUMBER: 125:269966
TITLE: Binding and internalization of the Helicobacter **pylori vacuolating cytotoxin** by epithelial cells
AUTHOR(S): Garner, Juli A.; Cover, Timothy L.
CORPORATE SOURCE: Department Medicine, Vanderbilt University School Medicine, Nashville, TN, 37232-2605, USA
SOURCE: Infection and Immunity (1996), 64(10), 4197-4203 CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Many Helicobacter **pylori** strains produce a **cytotoxin** (**VacA**) that induces **vacuolation** in epithelial cells. In this study, binding and internalization of the **cytotoxin** by HeLa or AGS (human gastric adenocarcinoma) cells were characterized by indirect fluorescence microscopy. Cells incubated with the **cytotoxin** at 4.degree.C displayed a uniform fluorescent plasma membrane signal. Preincubation of the **cytotoxin** with either rabbit antiserum to .apprx.90-kDda H. **pylori VacA** or sera from H. **pylori**-infected persons inhibited its binding to cells and blocked its capacity to induce cytoplasmic **vacuolation**. **Recombinant** VacA fragments (.apprx.34 and .apprx.58 kDa), corresponding to two proteolytic cleavage products of .apprx.90-kda VacA, each bound to the plasma membrane of HeLa cells. Antiserum reactive with the .apprx.58-kDa **VacA** fragment inhibited the binding of native H. **pylori cytotoxin** to cells and inhibited **cytotoxin** activity, whereas antiserum to the .apprx.34-kDa fragment had no effect. When incubated with cells at 37.degree.C for .gtoreq.3 h, the H. **pylori cytotoxin** localized intracellularly in a perinuclear location but did not localize within **cytotoxin**-induced **vacuoles**. When cells with previously bound **cytotoxin** were incubated with anticytotoxin serum at 4.degree.C and then shifted to 37.degree.C, **vacuolation** was completely inhibited. Bound **cytotoxin** became inaccessible to the neutralizing effects of antiserum after 60 to 120 min of incubation with cells at 37.degree.C. These data suggest a model in which (i) VacA binds to cells primarily via amino acid sequences in its 58-kDa fragment, (ii) VacA internalization occurs slowly in a temp.-dependent process, and (iii) VacA interacts with an intracellular target.

L7 ANSWER 19 OF 20 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:667824 HCAPLUS
DOCUMENT NUMBER: 119:267824
TITLE: Molecular characterization of the 128-kDa

immunodominant antigen of Helicobacter pylori associated with cytotoxicity and duodenal ulcer

AUTHOR(S): Covacci, Antonello; Censini, Stefano; Bugnoli, Massimo; Petracca, Roberto; Burroni, Daniela; Macchia, Giovanni; Massone, Annalisa; Papini, Emanuele; Xiang, Xhaoying; et al.

CORPORATE SOURCE: Immunobiol. Res. Inst. Siena, Siena, 53100, Italy

SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1993), 90(12), 5791-5
CODEN: PNASA6; ISSN: 0027-8424

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Helicobacter pylori has been assocd. with gastritis, peptic ulcer, and gastric adenocarcinoma. The authors report the nucleotide sequence and expression of an immunodominant antigen of H. pylori and the immune response to the antigen during disease. The antigen, named CagA (**cytotoxin**-assocd. gene A), is a hydrophilic, surface-exposed protein of 128 kDa produced by most clin. isolates. The size of the cagA gene and its protein varies in different strains by a mechanism that involves duplication of regions within the gene. Clin. isolates that do not produce the antigen do not have the gene and are unable to produce an active **vacuolating cytotoxin**. An ELISA to detect the immune response against a **recombinant** fragment of this protein detects 75.3% of patients with gastroduodenal diseases and 100% of patients with duodenal ulcer ($P < 0.0005$), suggesting that only bacteria harboring this protein are assocd. with disease.

L7 ANSWER 20 OF 20 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1993:464573 HCAPLUS

DOCUMENT NUMBER: 119:64573

TITLE: Cloning and expression of a high-molecular-mass major antigen of Helicobacter pylori: Evidence of linkage to **cytotoxin** production

AUTHOR(S): Tummuru, Murali K. R.; Cover, Timothy L.; Blaser, Martin J.

CORPORATE SOURCE: Sch. Med., Vanderbilt Univ., Nashville, TN, 37232-2605, USA

SOURCE: Infect. Immun. (1993), 61(5), 1799-809
CODEN: INFIBR; ISSN: 0019-9567

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A high-mol.-mass (120-128-kDa) H. pylori antigen has been assocd. with peptic ulcer disease. A bank of 40,000 random chromosomal fragments of H. pylori 84-183 was created by using .lambda.ZapII. Screening of this bank in Escherichia coli XL1-Blue with absorbed serum from an H. pylori-infected person permitted the isolation and purifn. of a clone with a 3.5-kb insert. Subcloning of this insert (pMC3) permitted the expression of a **recombinant** H. pylori protein that had a mass of .apprx.96 kDa and that was recognized by the human serum. Sera that were obtained from H. pylori-infected persons and that recognized the native 120-128-kDa H. pylori antigen recognized the **recombinant** 96-kDa pMC3 protein to a significantly greater extent than did sera that did not recognize the native H. pylori antigen. All 19 H. pylori isolates producing the 120-128-kDa antigen hybridized with pMC3; none of 13 nonproducers did so. Because all 15 isolates producing the

vacuolating cytotoxin hybridized with pMC3, the gene was called cagA (**cytotoxin**-assocd. gene). Sequence anal. of pMC3 identified an open reading frame of 859 amino acids, without a termination codon. Parallel screening of a .lambda.gt11 library with human serum revealed pos. plaques with identical 0.6-kb inserts and sequences matching the sequence of the downstream region of pMC3. To clone the full-length gene, the 0.6-kb fragment was used as a probe and a clone with a 2.7-kb insert was isolated from the .lambda.ZapII genomic library. Nucleotide sequencing of this insert (pYB2) revealed a 785-bp sequence that overlapped the downstream region of pMC3. Translation of the complete nucleotide sequence of cagA revealed an open reading frame of 1181 amino acids yielding a protein of 131,517 daltons. There was no significant homol. with any previously reported protein sequence. These findings indicate the cloning and characterization of a high-mol.-mass H. pylori antigen potentially assocd. with virulence and with **cytotoxin** prodn.

[redacted] MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, PHIC, PHIN, TOXCENTER' ENTERED AT 12:32:40 ON 04 SEP 2002)

L1 7 SEA FILE=REGISTRY ABB=ON PLU=ON ("CYTOTOXIN (HELICOBACTER PYLORI CLONE TOXEE1 PRECURSOR)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI GENE VACA FRAGMENT)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI GENE VACA PRECURSOR)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI PRECURSOR REDUCED)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI PRECURSOR)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI STRAIN 26695 VACUOLATING OPEN READING FRAME HP0887)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI STRAIN 87-203 GENE VACA FRAGMENT REDUCED)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI TYPE I GENE VACA)"/CN OR "CYTOTOXIN (HELICOBACTER PYLORI)"/CN)

L12 1741 SEA (L1 OR CT OR CYTOTOXIN OR CYTO TOXIN)(S) VACUOL?

[redacted] 42 SEA L12(S) RECOMBINAN?

L4 225 SEA FILE=HCAPLUS ABB=ON PLU=ON (VAC A OR VACA)(S)(CT OR CYTOTOXIN OR CYTO TOXIN)

L14 850 SEA L4(S)(HP OR PYLORI)

[redacted] 33 SEA L14(S) RECOMBINAN?

[redacted] 43 S L13 OR L15

PROCESSING COMPLETED FOR L16

[redacted] 17 DUP REM L16 (26 DUPLICATES REMOVED)

L17 ANSWER 1 OF 17 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002361835 MEDLINE
DOCUMENT NUMBER: 22077407 PubMed ID: 12082053
TITLE: An antibody to VacA of Helicobacter pylori in cerebrospinal fluid from patients with Guillain-Barre syndrome.
AUTHOR: Chiba S; Sugiyama T; Yonekura K; Tanaka S; Matsumoto H; Fujii N; Ebisu S; Sekiguchi K
CORPORATE SOURCE: Department of Neurology, School of Medicine, Sapporo Medical University, Sapporo, Japan.. chiba@sapmed.ac.jp
SOURCE: JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY,

(2002 Jul) 73 (1) 76-8.
Journal code: 2985191R. ISSN: 0022-3050.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020712
Last Updated on STN: 20020725
Entered Medline: 20020724

AB OBJECTIVE: To detect antibodies to **recombinant vacuolating cytotoxin** (r-**VacA**) of Helicobacter **pylori** in cerebrospinal fluid (CSF) from patients with Guillain-Barre syndrome (GBS). METHODS: CSF samples from 13 patients with GBS (electrophysiologically classified as eight acute inflammatory demyelinating polyradiculoneuropathy (AIDP), four acute motor axonal neuropathy (AMAN), and one unexcitable nerve conduction) and eight disease control patients were studied. The r-**VacA** protein was separated by SDS/PAGE, and Western blot analysis was carried out. RESULTS: Six of the 13 patients with GBS had a specific IgG antibody to **VacA** of H **pylori**, which was confirmed by absorption experiments using r-**VacA**. Every patient with positive CSF anti-r-**VacA** IgG had AIDP. CONCLUSION: The sequence homology previously found between **VacA** and human (Na(+)+K(+))-ATPase A subunit suggests that antibodies to **VacA** involve ion channels in abaxonal Schwann cell plasmalemma resulting in demyelination in some patients with GBS.

L17 ANSWER 2 OF 17 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 2001392820 MEDLINE
DOCUMENT NUMBER: 21340398 PubMed ID: 11447189
TITLE: Vacuolating cytotoxin of Helicobacter pylori induces apoptosis in the human gastric epithelial cell line AGS.
AUTHOR: Kuck D; Kolmerer B; Iking-Konert C; Krammer P H; Stremmel W; Rudi J
CORPORATE SOURCE: Department of Medicine, University of Heidelberg, 69115 Heidelberg, Germany.
SOURCE: INFECTION AND IMMUNITY, (2001 Aug) 69 (8) 5080-7.
Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010827
Last Updated on STN: 20010827
Entered Medline: 20010823

AB Helicobacter **pylori** induces cell death by apoptosis. However, the apoptosis-inducing factor is still unknown. The virulence factor **vacuolating cytotoxin** A (**VacA**) is a potential candidate, and thus its role in apoptosis induction was investigated in the human gastric epithelial cell line AGS. The supernatant from the **vacA** wild-type strain P12 was able to induce apoptotic cell death, whereas the supernatant from its isogenic mutant strain P14 could not. That **VacA** was indeed the apoptosis-inducing factor was

demonstrated further by substantial reduction of apoptosis upon treatment of AGS cells with a supernatant specifically depleted of native **VacA**. Furthermore, a **recombinant VacA** produced in Escherichia coli was also able to induce apoptosis in AGS cells but failed to induce cellular **vacuolation**. These findings demonstrate that the **vacuolating** cytototoxin of H. **pylori** is a bacterial factor capable of inducing apoptosis in gastric epithelial cells.

L17 ANSWER 3 OF 17 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001169732 MEDLINE
DOCUMENT NUMBER: 21167502 PubMed ID: 11267842
TITLE: Helicobacter pylori vacuolating cytotoxin binding to a putative cell surface receptor, heparan sulfate, studied by surface plasmon resonance.
AUTHOR: Utt M; Danielsson B; Wadstrom T
CORPORATE SOURCE: Department of Infectious Diseases and Medical Microbiology, Lund University, Solvegatan, Lund, Sweden.
SOURCE: FEMS IMMUNOLOGY AND MEDICAL MICROBIOLOGY, (2001 Mar) 30 (2) 109-13.
Journal code: 9315554. ISSN: 0928-8244.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010529
Last Updated on STN: 20010529
Entered Medline: 20010524

AB The Helicobacter **pylori vacuolating cytotoxin** or **VacA** toxin is a major virulence factor in H. **pylori** infection and type B gastritis. We predicted heparin/heparan sulfate (H/HS) binding properties of the 58-kDa subunit of **VacA cytotoxin** using bioinformatics tools and showed this by surface plasmon resonance (SPR)-based biosensor studies. Putative H/HS binding peptides were synthesized and binding to HS was shown by SPR in the absence or presence of trifluoroethanol. We found that a **recombinant cytotoxin VacA** polypeptide binds to surface-immobilized HS and propose that HS might be a receptor/co-receptor for H. **pylori VacA cytotoxin**.

L17 ANSWER 4 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:166834 BIOSIS
DOCUMENT NUMBER: PREV200100166834
TITLE: Antibody against recombinant Vac-A of Helicobacter pylori was detected in the cerebrospinal fluid obtained from patients with Guillain-Barre syndrome.
AUTHOR(S): Chiba, S. (1); Sugiyama, T.; Hiura, K.; Saitoh, M.; Matsumoto, H.; Fujii, N.; Ebisu, S.; Sekiguchi
CORPORATE SOURCE: (1) School of Medicine, Sapporo Medical University, Sapporo Japan
SOURCE: Gut, (October, 2000) Vol. 47, No. Supplement 1, pp. A91. print.
Meeting Info.: XIIIth International Workshop on

Gastroduodenal Pathology and Helicobacter pylori
Rome, Italy October 11-14, 2000
ISSN: 0017-5749.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L17 ANSWER 5 OF 17 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1999389369 MEDLINE
DOCUMENT NUMBER: 99389369 PubMed ID: 10462273
TITLE: Epidemiology of Helicobacter pylori in chronic haemodialysis patients using the new RIBA H. pylori SIA.
AUTHOR: Fabrizi F; Martin P; Dixit V; Quan S; Brezina M; Abbey H; Gerosa S; Kaufman E; DiNello R; Polito A; Gitnick G
CORPORATE SOURCE: Division of Digestive Diseases, UCLA School of Medicine, Los Angeles, CA, USA.
SOURCE: NEPHROLOGY, DIALYSIS, TRANSPLANTATION, (1999 Aug) 14 (8) 1929-33.
Journal code: 8706402. ISSN: 0931-0509.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991008

AB BACKGROUND: There are few data concerning the epidemiology of H. **pylori** in patients on chronic haemodialysis (HD) treatment. These surveys concerned small populations and were made with ELISA technique. However, ELISA-based assays do not differentiate between strains of H. **pylori** that are associated with ulcers. Recent literature reports that formation of ulcers correlates strongly with the expression of **cytotoxin**-associated protein (CagA) and **vacuolating cytotoxin** (**VacA**) of H. **pylori**. METHODS: A novel serological test (RIBA H. **pylori** strip immunoblot assay (SIA)) has been recently introduced, it uses the H. **pylori** lysate (Lys) along with two additional purified **recombinant** antigens derived from CagA and **VacA** of H. **pylori** . AIM: To study the epidemiology of H. **pylori** using RIBA H. **pylori** SIA among chronic HD patients and blood donors as a control group. In addition, the activity of H. **pylori** was analysed by immunoblot technique in a group of patients with documented ulcers and normal renal function. RESULTS: The prevalence of antibody towards H. **pylori** among HD patients, blood donors, and patients with documented ulcers was 56% (127/228), 53% (84/158), and 100%, (21/21) respectively; the difference was significant (P=0.0001). The frequency of anti-H. **pylori** -positive individuals was significantly higher in patients with documented ulcers than HD patients and blood donors, 21/21 (100%) vs 211/386 (55%), P=0.0001. The frequency of antibody to H. **pylori** in the HD population was significantly associated with race (P= 0.005); no relationship between anti-H. **pylori** antibody and numerous demographic, biochemical, and clinical features of patients was seen. The frequency of antibodies against

virulent strains of H. **pylori** in HD patients and blood donors with H. **pylori** was 60% (76/127) and 61% (51/84) respectively; it was 86% (18/21) among individuals with documented ulcers. No significant difference among these three groups occurred. CONCLUSIONS: The frequency of antibody towards H. **pylori** by RIBA H. **pylori** SIA was high both in HD patients and blood donors; patients with documented ulcers and normal renal function had significantly higher frequency of anti-H. **pylori** antibody. The anti-H. **pylori** antibody rate among HD patients was strongly associated with race. The prevalence of antibody against virulent strains of H. **pylori** did not change among HD patients and control groups. Studies in large cohorts of HD patients with documented peptic ulcer disease are in progress.

L17 ANSWER 6 OF 17 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999442307 MEDLINE
DOCUMENT NUMBER: 99442307 PubMed ID: 10514122
TITLE: VacA seropositivity is not associated with the development of gastric cancer in a Japanese population.
AUTHOR: Shimoyama T; Neelam B; Fukuda S; Tanaka M; Munakata A; Crabtree J E
CORPORATE SOURCE: Molecular Medicine Unit, St James's University Hospital, Leeds, UK.
SOURCE: EUROPEAN JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY, (1999 Aug) 11 (8) 887-90.
Journal code: 9000874. ISSN: 0954-691X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991119

AB OBJECTIVES: Infection with Helicobacter **pylori** strains producing **vacuolating cytotoxin** (**VacA**) is associated with enhanced gastric mucosal damage and the development of gastric mucosal atrophy. The aim of this study was to investigate whether **VacA** seropositivity is associated with increasing risk of gastric cancer in Japanese populations which have much higher incidence of gastric cancer than Western populations. METHODS: Serum sample was collected from 81 patients with gastric cancer and 81 sex- and age-matched endoscopically evaluated control subjects. Histologically, 62 cancers were of the intestinal type and 76 were early gastric cancer. H. **pylori** and **VacA** IgG antibodies were assayed by Western blotting using Chiron Diagnostics' **Recombinant** Immunoblot Assay (RIBAa). RESULTS: **VacA** seropositivity was 68% (55/81) in patients with gastric cancer and 70% (57/81) in controls. The odds ratio for the risk of gastric cancer in **VacA** seropositives was 0.89 (95% CI 0.46-1.74). In H. **pylori** seropositive patients and their control subjects (matched H. **pylori**-positive controls), **VacA** seropositivity was the same 80.6% (50/62). The odds ratio for the risk of gastric cancer in H. **pylori** -positive patients if **VacA** seropositive was 1.00 (95% CI 0.41-2.44). The mean relative intensity of **VacA** antibody

titre was 3.01+/-0.18 in the 55 **VacA** seropositive cancer patients and 3.09+/-0.17 in the 57 **VacA** seropositive control subjects (difference not significant). CONCLUSION: These results suggest that **VacA** seropositivity is not associated with increasing risk of gastric cancer in Japanese populations.

L17 ANSWER 7 OF 17 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000055755 MEDLINE
DOCUMENT NUMBER: 20055755 PubMed ID: 10589838
TITLE: A plasmid-based vector system for the cloning and expression of Helicobacter pylori genes encoding outer membrane proteins.
AUTHOR: Fischer W; Schwan D; Gerland E; Erlenfeld G E; Odenbreit S; Haas R
CORPORATE SOURCE: Max von Pettenkofer-Institut fur Hygiene und Medizinische Mikrobiologie, Ludwig-Maximilians-Universitat, Munchen, Germany.. schmitt@m3401.mpk.med.uni-muenchen.de
SOURCE: MOLECULAR AND GENERAL GENETICS, (1999 Oct) 262 (3) 501-7.
Journal code: 0125036. ISSN: 0026-8925.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991228

AB Helicobacter **pylori** produces a number of proteins associated with the outer membrane, including adhesins and the **vacuolating cytotoxin**. We observed that the functional expression of such proteins is deleterious to Escherichia coli, the host bacterium used for gene cloning. Therefore, a general method was developed for the functional expression of such genes on a shuttle vector in H. **pylori**, which has been termed SOMPES (Shuttle vector-based Outer Membrane Protein Expression System). The intact, active gene is reconstituted by recombination in H. **pylori** from partial gene sequences cloned on an E. coli-H. **pylori** shuttle vector. This system was established in an H. **pylori** strain carrying a precise, unmarked chromosomal deletion of the **vacA** gene, which was constructed by adapting the streptomycin sensitivity system to H. **pylori**. It is based on the expression of the H. **pylori** rpsL gene as a counterselectable marker in the genetic background of an rpsL mutant. The utility of this approach is demonstrated by the expression of a **recombinant** gene encoding **vacuolating cytotoxin** (**vacA**) and a **recombinant** gene encoding an adherence-associated outer membrane protein (alpA) in H. **pylori**.

L17 ANSWER 8 OF 17 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1999165056 MEDLINE
DOCUMENT NUMBER: 99165056 PubMed ID: 10067733
TITLE: Helicobacter pylori and type 1 diabetes mellitus in children.
AUTHOR: Salardi S; Cacciari E; Menegatti M; Landi F; Mazzanti L; Stella F A; Pirazzoli P; Vaira D

CORPORATE SOURCE: First Pediatric Clinic, University of Bologna, Italy.
SOURCE: JOURNAL OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION, (1999 Mar) 28 (3) 307-9.
Journal code: 8211545. ISSN: 0277-2116.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 19990511
Entered Medline: 19990429

AB BACKGROUND: Helicobacter **pylori** is a recognized gastroduodenal pathogen and H. **pylori** infection is one of the most common bacterial infections, usually acquired during childhood. However, diabetes mellitus is characterized by an increased susceptibility to infections. METHODS: We compared the prevalence of H. **pylori** infection as well as **cytotoxin**-associated gene A-CagA-and **vacuolating cytotoxin** gene A-**VacA**-positivity in 103 children and adolescents with type 1 diabetes mellitus and in 236 nondiabetic children. We used a novel **Recombinant** ImmunoBlot Assay-Strip (RIBA SIA) with individual band for whole H. **pylori** lysate and **recombinant** CagA and **VacA**. RESULTS: H. **pylori**-positive subjects, both diabetics and controls, were significantly older than negative subjects. In the whole group of diabetic patients the prevalence of each of the three reactivities was higher than in control subjects, reaching significance only for lysate. Only diabetic patients over 12 years of age, with a longer disease duration, had a higher prevalence of positive cases, although not significantly so. CONCLUSIONS: In the first few years of disease, diabetic children do not differ from the nondiabetic population. Subsequently they show an H. **pylori** seroprevalence tendentially higher than that of controls of the same age. Therefore, H. **pylori** infection acquired in childhood and lasting several years, could be one of the causes of chronic atrophic gastritis, which is more frequent in longstanding diabetes mellitus.

L17 ANSWER 9 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:496111 BIOSIS
DOCUMENT NUMBER: PREV199900496111
TITLE: Production of active, **recombinant vacuolating cytotoxin** in Helicobacter pylori and outer membrane targeting of passenger proteins by the **cytotoxin** autotransporter.
AUTHOR(S): Fischer, W. (1); Schwan, D. (1); Gerland, E. (1); Erlenfeld, G. E. (1); Odenbreit, S. (1); Haas, R. (1)
CORPORATE SOURCE: (1) Max von Pettenkofer Institute for Hygiene and Medical Microbiology, Munich Germany
SOURCE: Gut, (Sept., 1999) Vol. 45, No. SUPPL. 3, pp. A18.
Meeting Info.: XIIth International Workshop on Gastroduodenal Pathology and Helicobacter pylori Helsinki, Finland September 2-4, 1999
ISSN: 0017-5749.
DOCUMENT TYPE: Conference
LANGUAGE: English

L17 ANSWER 10 OF 17 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1998238199 MEDLINE
DOCUMENT NUMBER: 98238199 PubMed ID: 9577338
TITLE: Major virulence factors, VacA and CagA, are commonly positive in Helicobacter pylori isolates in Japan.
AUTHOR: Maeda S; Ogura K; Yoshida H; Kanai F; Ikenoue T; Kato N; Shiratori Y; Omata M
CORPORATE SOURCE: Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Japan.
SOURCE: GUT, (1998 Mar) 42 (3) 338-43.
Journal code: 2985108R. ISSN: 0017-5749.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980520
Last Updated on STN: 19990129
Entered Medline: 19980514

AB BACKGROUND: **VacA** and CagA proteins have been reported to be major virulence factors of Helicobacter **pylori**. However, antibodies against these proteins are frequently found in the sera of Japanese patients regardless of their gastroduodenal status. AIM: To evaluate the expression of **VacA** and CagA proteins by H **pylori** strains isolated in Japan. METHODS: By using specific antibodies raised against **recombinant VacA** and CagA proteins, the expression of **VacA** and CagA was evaluated in 68 H **pylori** strains isolated from Japanese patients; a **vacuolating** assay and genotyping of the **vacA** gene were also used in the evaluation. The results in analysed in relation to the gastroduodenal diseases of the hosts. RESULTS: **VacA** and CagA proteins were expressed in 59/68 (87%) and in 61/68 (90%) isolates respectively. The **vacuolating** assay was positive in 57/68 (84%) isolates, indicating that most immunologically **VacA** positive strains produced active **cytotoxin**. The prevalence of infection with strains expressing CagA and positive for **vacuolating** activity (Type I) was very high, 54/68 (79%), irrespective of the gastroduodenal status of the host. CONCLUSION: Most H **pylori** isolates in Japan are positive for **vacuolating cytotoxin** and CagA, and thus these virulence factors cannot be used as markers to discern the risk of developing serious gastroduodenal pathologies in the hosts. However, the high prevalence of infection with strains positive for **vacuolating cytotoxin** and CagA may contribute to the characteristics of H **pylori** infection in Japan.

L17 ANSWER 11 OF 17 MEDLINE
ACCESSION NUMBER: 1999062052 MEDLINE
DOCUMENT NUMBER: 99062052 PubMed ID: 9844065
TITLE: Relationship of vacA genotypes of Helicobacter pylori to cagA status, cytotoxin production, and clinical outcome.
AUTHOR: Yamaoka Y; Kodama T; Kita M; Imanishi J; Kashima K; Graham D Y
CORPORATE SOURCE: Department of Medicine, Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Texas

77030, USA.. yyamaoka@bcm.tmc.edu
SOURCE: HELICOBACTER, (1998 Dec) 3 (4) 241-53.
Journal code: 9605411. ISSN: 1083-4389.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990126

AB. BACKGROUND: Mosaicism in **vacA** alleles with three distinct families of **vacA** signal sequences (s1a, s1b and s2) and two distinct families of middle region alleles (m1 and m2) has been reported. It was suggested that the **vacA** s1a genotype was closely associated with duodenal ulcer disease and with high **cytotoxin** production. The aim of this study was to evaluate the role of **vacA** genotyping with respect to gastric inflammation and injury, **cytotoxin** activity, and clinical presentation. METHODS: H. **pylori** from patients with gastritis, peptic ulcer disease, or gastric cancer were characterized by **vacA** typing by polymerase chain reaction (PCR) and DNA sequencing. In vitro **cytotoxin** activity was assessed by **vacuolation** assay using Vero cells as well as with Hela cells. RESULTS: Four hundred ninety-one strains were tested. **vacA** genotype s1a/m1 was present in more than 95% of strains independent of presentation with gastritis, peptic ulcer, or gastric cancer. No **vacA** genotype was associated with high average **cytotoxin** activity. The s2/m2 isolates had low or absent **cytotoxin** activity. All cagA negative strains (n = 18) were s1a strains and both s2/m2 strains were cagA positive. One strain that was a **recombinant** of m1 and m2 strains was identified and had low **cytotoxin** activity. The nucleotide and amino acid sequences between original m1 strains and Japanese m1 strains (new m1 strains) were about 85% and 81%, respectively. Strains with the new m1 genotype had nucleotide and amino acid sequences similarity of more than 96%. There was no difference in **cytotoxin** activity between strains with the Western type m1 and the new type m1 genotype. CONCLUSION: In this as in other reported studies (approximately 1500 patients overall) **vacA** genotype was strongly but not exclusively associated with the presence of cagA. Overall, the studies did not support a role for **vacA** genotyping in relation to **cytotoxin** activity, virulence, histologic finding, or risk of a particular H. **pylori** disease. **vacA** genotype s1 is likely to be a surrogate marker for the presence of the cag pathogenicity island.

L17 ANSWER 12 OF 17 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1998-434923 [37] WPIDS
TITLE: Method for producing **vacuolating** **cytotoxin** of helicobacter pylori from **recombinant** coli NoAbstract.
DERWENT CLASS: B04 D16
INVENTOR(S): CHANG, H; KIM, C; YOO, Y; CHANG, H J; KIM, C H; YOO, Y J
PATENT ASSIGNEE(S): (GLDS) LG CHEM CO LTD; (GLDS) LG CHEM LTD
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
KR 97059276	A	19970812	(199837)*		
KR 210508	B1	19990715	(200102)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
KR 97059276	A	KR 1996-1197	19960120
KR 210508	B1	KR 1996-1197	19960120

PRIORITY APPLN. INFO: KR 1996-1197 19960120
**** DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L17 ANSWER 13 OF 17 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 1998052632 MEDLINE
DOCUMENT NUMBER: 98052632 PubMed ID: 9391243
TITLE: High prevalence of cytotoxin positive Helicobacter pylori in patients unrelated to the presence of peptic ulcers in Japan.
AUTHOR: Ogura K; Kanai F; Maeda S; Yoshida H; Ogura M; Lan K H; Hirota K; Kawabe T; Shiratori Y; Omata M
CORPORATE SOURCE: Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Japan.
SOURCE: GUT, (1997 Oct) 41 (4) 463-8.
Journal code: 2985108R. ISSN: 0017-5749.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971217

AB BACKGROUND: It has been reported that infection with **vacuolating cytotoxin** positive Helicobacter **pylori** strains is associated with gastroduodenal disease in Western countries. AIMS: To evaluate the prevalence of **cytotoxin** producing strains among patients with H **pylori** infection in relation to gastrointestinal diseases in Japan. PATIENTS: Ninety seven patients undergoing endoscopy. METHODS: A Western blot assay was conducted to detect serum antibodies against the **cytotoxin** using **recombinant cytotoxin** (**VacA** protein) as an antigen. To obtain a purified **recombinant cytotoxin**, the **vacA** gene (2233 nucleotides) was cloned into an expression vector to produce the protein (744 amino acids), which was expressed in Escherichia coli. RESULTS: Serum IgG antibodies to the **cytotoxin** were present in 85%, 95%, 95%, and 100% of infected patients with gastric ulcer (n = 26), duodenal ulcer (n = 21), chronic gastritis (n = 19), and endoscopically normal mucosa (n = 14), respectively. CONCLUSION: The western blot method using **recombinant VacA** protein is simple and useful for detecting antibody to **vacuolating cytotoxin**. This method showed antibodies against **cytotoxin** were

highly prevalent, even in subjects with endoscopically normal mucosa in Japan, indicating that the **cytotoxin** may not be an independent cause of gastrointestinal diseases induced by H **pylori** infection.

L17 ANSWER 14 OF 17 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 97047699 MEDLINE
DOCUMENT NUMBER: 97047699 PubMed ID: 8926088
TITLE: Binding and internalization of the Helicobacter pylori vacuolating cytotoxin by epithelial cells.
AUTHOR: Garner J A; Cover T L
CORPORATE SOURCE: Division of Infectious Diseases, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-2605, USA.
CONTRACT NUMBER: R01-AI39657 (NIAID)
R29-AK45293
SOURCE: INFECTION AND IMMUNITY, (1996 Oct) 64 (10) 4197-203.
Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961114

AB Many Helicobacter **pylori** strains produce a **cytotoxin** (**VacA**) that induces **vacuolation** in epithelial cells. In this study, binding and internalization of the **cytotoxin** by HeLa or AGS (human gastric adenocarcinoma) cells were characterized by indirect fluorescence microscopy. Cells incubated with the **cytotoxin** at 4 degrees C displayed a uniform fluorescent plasma membrane signal. Preincubation of the **cytotoxin** with either rabbit antiserum to approximately 90-kDa H. **pylori VacA** or sera from H. **pylori**-infected persons inhibited its binding to cells and blocked its capacity to induce cytoplasmic **vacuolation**. **Recombinant VacA** fragments (approximately 34 and approximately 58 kDa), corresponding to two proteolytic cleavage products of approximately 90-kDa **VacA** , each bound to the plasma membrane of HeLa cells. Antiserum reactive with the approximately 58-kDa **VacA** fragment inhibited the binding of native H. **pylori cytotoxin** to cells and inhibited **cytotoxin** activity, whereas antiserum to the approximately 34-kDa fragment had no effect. When incubated with cells at 37 degrees C for > or = 3 h, the H. **pylori cytotoxin** localized intracellularly in a perinuclear location but did not localize within **cytotoxin**-induced **vacuoles**. When cells with previously bound **cytotoxin** were incubated with anticytotoxin serum at 4 degrees C and then shifted to 37 degrees C, **vacuolation** was completely inhibited. Bound **cytotoxin** became inaccessible to the neutralizing effects of antiserum after 60 to 120 min of incubation with cells at 37 degrees C. These data suggest a model in which (i) **VacA** binds to cells primarily via amino acid sequences in its 58-kDa fragment, (ii) **VacA** internalization occurs slowly in a temperature-dependent process, and (iii) **VacA** interacts

with an intracellular target.

L17 ANSWER 15 OF 17 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 93296225 MEDLINE
DOCUMENT NUMBER: 93296225 PubMed ID: 8516329
TITLE: Molecular characterization of the 128-kDa immunodominant antigen of Helicobacter pylori associated with cytotoxicity and duodenal ulcer.
AUTHOR: Covacci A; Censini S; Bugnoli M; Petracca R; Burroni D; Macchia G; Massone A; Papini E; Xiang Z; Figura N; +
CORPORATE SOURCE: Immunobiological Research Institute Siena, Italy.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1993 Jun 15) 90 (12) 5791-5.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-X70038; GENBANK-X70039
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930806
Last Updated on STN: 19990129
Entered Medline: 19930722

AB Helicobacter pylori has been associated with gastritis, peptic ulcer, and gastric adenocarcinoma. We report the nucleotide sequence and expression of an immunodominant antigen of H. pylori and the immune response to the antigen during disease. The antigen, named CagA (**cytotoxin**-associated gene A), is a hydrophilic, surface-exposed protein of 128 kDa produced by most clinical isolates. The size of the cagA gene and its protein varies in different strains by a mechanism that involves duplication of regions within the gene. Clinical isolates that do not produce the antigen do not have the gene and are unable to produce an active **vacuolating cytotoxin**. An ELISA to detect the immune response against a **recombinant** fragment of this protein detects 75.3% of patients with gastroduodenal diseases and 100% of patients with duodenal ulcer ($P < 0.0005$), suggesting that only bacteria harboring this protein are associated with disease.

L17 ANSWER 16 OF 17 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 93239281 MEDLINE
DOCUMENT NUMBER: 93239281 PubMed ID: 8478069
TITLE: Cloning and expression of a high-molecular-mass major antigen of Helicobacter pylori: evidence of linkage to cytotoxin production.
AUTHOR: Tummuru M K; Cover T L; Blaser M J
CORPORATE SOURCE: Department of Medicine, Vanderbilt Unviersity School of Medicine, Nashville, Tennessee 37232-2605.
SOURCE: INFECTION AND IMMUNITY, (1993 May) 61 (5) 1799-809.
Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-L11714
ENTRY MONTH: 199305

ENTRY DATE: Entered STN: 19930611
Last Updated on STN: 19990129
Entered Medline: 19930524

AB A high-molecular-mass (120- to 128-kDa) Helicobacter pylori antigen has been associated with peptic ulcer disease. We created a bank of 40,000 random chromosomal fragments of H. pylori 84-183 by using lambda ZapII. Screening of this bank in Escherichia coli XL1-Blue with absorbed serum from an H. pylori-infected person permitted the isolation and purification of a clone with a 3.5-kb insert. Subcloning of this insert (pMC3) permitted the expression of a **recombinant** H. pylori protein that had a mass of approximately 96 kDa and that was recognized by the human serum. Sera that were obtained from H. pylori-infected persons and that recognized the native 120- to 128-kDa H. pylori antigen recognized the **recombinant** 96-kDa pMC3 protein to a significantly greater extent than did sera that did not recognize the native H. pylori antigen. All 19 H. pylori isolates producing the 120- to 128-kDa antigen hybridized with pMC3; none of 13 nonproducers did so ($P < 0.001$). Because all 15 isolates producing the **vacuolating cytotoxin** hybridized with pMC3, we called the gene cagA (**cytotoxin**-associated gene). Sequence analysis of pMC3 identified an open reading frame of 859 amino acids, without a termination codon. Parallel screening of a lambda gt11 library with human serum revealed positive plaques with identical 0.6-kb inserts and sequences matching the sequence of the downstream region of pMC3. To clone the full-length gene, we used the 0.6-kb fragment as a probe and isolated a clone with a 2.7-kb insert from the lambda ZapII genomic library. Nucleotide sequencing of this insert (pYB 2) revealed a 785-bp sequence that overlapped the downstream region of pMC3. Translation of the complete nucleotide sequence of cagA revealed an open reading frame of 1,181 amino acids yielding a protein of 131,517 daltons. There was no significant homology with any previously reported protein sequence. These findings indicate the cloning and characterization of a high-molecular-mass H. pylori antigen potentially associated with virulence and with **cytotoxin** production.

L17 ANSWER 17 OF 17 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93313061 EMBASE
DOCUMENT NUMBER: 1993313061
TITLE: Molecular analysis of the Helicobacter pylori cytotoxin gene.
AUTHOR: Telford J.L.; Dell'Orco M.; Burroni D.; Comanducci M.; Bugnoli M.; Figura N.; Covacci A.; Rappuoli R.
CORPORATE SOURCE: Immunology Research Institute Siena, Via Fiorentina 1,53100 Siena, Italy
SOURCE: European Journal of Gastroenterology and Hepatology, (1993) 5/SUPPL. 2 (S22-S24).
ISSN: 0954-691X CODEN: EJGHES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objective: To assess the contribution of the **vacuolating cytotoxin** to Helicobacter pylori virulence. Design: Approximately 50% of clinical isolates of H. pylori produce a potent **vacuolating cytotoxin** and a **cytotoxin**

-associated protein with a molecular weight of 128 000 (CagA). A molecular genetic analysis of **cytotoxin**-positive and -negative strains was performed to clarify the effects of this **cytotoxin** in H. pylori virulence. Methods: We used the polymerase chain reaction and molecular cloning to obtain the gene coding for the **cytotoxin**. **Cytotoxin**-positive and -negative strains of H. pylori were analysed by DNA hybridization and the use of antisera raised against the **recombinant cytotoxin**. Results: We cloned the entire gene coding for the **cytotoxin** and raised antisera against the gene product. This gene proved to be unrelated to the gene coding for the **cytotoxin**-associated protein (cagA gene). The protein was not produced by **cytotoxin**-negative strains of H. pylori, although cagA gene sequences were present in the genome. Conclusions: Although the cagA gene was absent in **cytotoxin** -negative H. pylori strains, the **cytotoxin** gene was present, but not expressed, suggesting that the cagA gene may regulate cytotoxicity.

FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, PHIC, PHIN, TOXCENTER' ENTERED AT 12:42:54 ON 04 SEP 2002

- Author(s)

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L18          354 SEA ABB=ON  PLU=ON  "COVACCI A"?/AU
L19          209 SEA ABB=ON  PLU=ON  "BUGNOLI M"?/AU
L20         1002 SEA ABB=ON  PLU=ON  "TELFORD J"?/AU
L21         2108 SEA ABB=ON  PLU=ON  "RAPPUOLI R"?/AU
L22          233 SEA ABB=ON  PLU=ON  "MACCHIA G"?/AU
L23           10 SEA ABB=ON  PLU=ON  L18 AND L19 AND L20 AND L21 AND L22

L24          200 SEA ABB=ON  PLU=ON  L18 AND (L19 OR L20 OR L21 OR L22)
L25          117 SEA ABB=ON  PLU=ON  L19 AND (L20 OR L21 OR L22)
L26          299 SEA ABB=ON  PLU=ON  L20 AND (L21 OR L22 OR L23)
L27           16 SEA ABB=ON  PLU=ON  L21 AND (L22 OR L23)
L28           10 SEA ABB=ON  PLU=ON  L22 AND L23
L29          253 SEA ABB=ON  PLU=ON  (L24 OR L25 OR L26 OR L18 OR L19 OR
                 L20 OR L21 OR L22) AND (L2 OR L4)
L30           21 SEA ABB=ON  PLU=ON  L29 AND RECOMBINAN?
L31           36 SEA ABB=ON  PLU=ON  L23 OR L27 OR L28 OR L30
L32           18 DUP REM L31 (18 DUPLICATES REMOVED)
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L32 ANSWER 1 OF 18 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:239751 BIOSIS
DOCUMENT NUMBER: PREV200100239751
TITLE: Helicobacter pylori proteins useful for vaccines and diagnostics.
AUTHOR(S): **Covacci, Antonello (1); Bugnoli, Massimo; Telford, John; Macchia, Giovanni; Rappuoli, Rino**
CORPORATE SOURCE: (1) Vc.Provenzano, 8, 53100, Siena Italy
PATENT INFORMATION: US 6130059 October 10, 2000
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Oct. 10, 2000) Vol. 1239, No. 2, pp. No Pagination. e-file. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English

AB Helicobacter pylori is known to cause or be a cofactor in type B gastritis, peptic ulcers, and gastric tumors. In both developed and developing countries, a high percentage of people are infected with

this bacterium. The present invention relates generally to certain H. pylori proteins, to the genes which express these proteins, and to the use of these proteins for diagnostic and vaccine applications. Specifically, molecular cloning, nucteotide, and amino acid sequences for the H. pylori cytotoxin (CT), the "Cytotoxin Associated Immunodominant" (CAI) antigen, and the heat shock protein (hsp60). are described herein.

L32 ANSWER 2 OF 18 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:181462 BIOSIS
DOCUMENT NUMBER: PREV200100181462
TITLE: Helicobacter pylori proteins useful for vaccines and diagnostics.
AUTHOR(S): **Covacci, Antonello (1); Bugnoli, Massimo; Telford, John; Macchia, Giovanni; Rappuoli, Rino**
CORPORATE SOURCE: (1) Siena Italy
ASSIGNEE: Chiron S.p.A., Siena, Italy
PATENT INFORMATION: US 6090611 July 18, 2000
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (July 18, 2000) Vol. 1236, No. 3, pp. No Pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB A cytotoxin associated immunodominant antigen and the nucleic acid encoding the antigen from Helicobacter pylori are described. This antigen was identified from the cytotoxin positive CCUG 17874 Helicobacter pylori strain, and both the antigen and the DNA encoding it have been sequenced. The antigen is a hydrophilic, surface-exposed protein having a molecular weight of 120-132 kDa. The nucleic acid encoding the antigen may be incorporated into a vector for transformation of host cells for expression of the antigen. Both the DNA and the antigen can be used in assays for detection of disease or infection by Helicobacter pylori, and may find use in treating and preventing infection by Helicobacter pylori and the diseases associated with such infection.

L32 ANSWER 3 OF 18 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:110167 BIOSIS
DOCUMENT NUMBER: PREV200100110167
TITLE: Helicobacter pylori proteins useful for vaccines and diagnostics.
AUTHOR(S): **Covacci, Antonello (1); Bugnoli, Massimo; Telford, John; Macchia, Giovanni; Rappuoli, Rino**
CORPORATE SOURCE: (1) Siena Italy
ASSIGNEE: Chiron Corporation
PATENT INFORMATION: US 6077706 June 20, 2000
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (June 20, 2000) Vol. 1235, No. 3, pp. No Pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB Helicobacter pylori known to cause or be a cofactor in type B gastritis, peptic ulcers, and gastric tumors. In both developed and developing countries, a high percentage of people are infected with

this bacterium. The present invention relates generally to certain H. pylori proteins, to the genes which express these proteins, and to the use of these proteins for diagnostic and vaccine applications. Specifically, molecular cloning, nucleotide, and amino add sequences for the H. pylori cytotoxin (CT), the "Cytotoxin Associated Immunodominant" (CAI) antigen, and the heat shock protein (hsp60) are described herein.

L32 ANSWER 4 OF 18 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1999321986 MEDLINE
DOCUMENT NUMBER: 99321986 PubMed ID: 10390344
TITLE: 3D imaging of the 58 kDa cell binding subunit of the Helicobacter pylori **cytotoxin**.
AUTHOR: Reyrat J M; Lanzavecchia S; Lupetti P; de Bernard M; Pagliaccia C; Pelicic V; Charrel M; Ulivieri C; Norais N; Ji X; Cabiaux V; Papini E; **Rappuoli R; Telford J L**
CORPORATE SOURCE: Chiron S.p.A., IRIS, via Fiorentina 1, Siena, 53100, Italy.
SOURCE: JOURNAL OF MOLECULAR BIOLOGY, (1999 Jul 9) 290 (2) 459-70.
Journal code: 2985088R. ISSN: 0022-2836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF050318; GENBANK-AF050395; GENBANK-AF050396
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990816
Last Updated on STN: 19990816
Entered Medline: 19990730

AB Pathogenic strains of Helicobacter pylori produce a potent exotoxin, VacA, which intoxicates gastric epithelial cells and leads to peptic ulcer. The toxin is released from the bacteria as a high molecular mass homo-oligomer of a 95 kDa polypeptide which undergoes specific proteolytic cleavage to 37 kDa and 58 kDa subunits. We have engineered a strain of H. pylori to delete the gene sequence coding for the 37 kDa subunit. The remaining 58 kDa subunit is expressed efficiently and exported as a soluble dimer that is non-toxic but binds target cells in a manner similar to the holotoxin. A 3D reconstruction of the molecule from electron micrographs of quick-freeze, deep-etched preparations reveals the contribution of each building block to the structure and permits the reconstruction of the oligomeric holotoxin starting from individual subunits. In this model P58 subunits are assembled in a ring structure with P37 subunits laying on the top. The data indicate that the 58 kDa subunit is capable of folding autonomously into a discrete structure recognizable within the holotoxin and containing the cell binding domain.

L32 ANSWER 5 OF 18 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999177476 MEDLINE
DOCUMENT NUMBER: 99177476 PubMed ID: 10077750
TITLE: Experimental model of Helicobacter pylori infection.
AUTHOR: Del Giudice G; Ghiara P; **Rappuoli R**
CORPORATE SOURCE: IRIS, Chiron Vaccines Immunobiological Research Institute in Siena, Italy.

SOURCE: ITALIAN JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY, (1998 Oct) 30 Suppl 3 S261-3. Ref: 15
Journal code: 9711056. ISSN: 1125-8055.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 19990511
Entered Medline: 19990426

AB Critical issues in the development of a vaccine against Helicobacter pylori are represented by the definition of molecules important in the pathogenesis of the infection, by the availability of an animal model reproducing several aspects of the human infection, and lastly by the availability of powerful adjuvants allowing strong protection after mucosal delivery of the antigens. A mouse model of Helicobacter pylori infection was established in our laboratories. Vaccination of these animals with Helicobacter pylori antigens, such as VacA, CagA, etc., induced protection, both prophylactic and therapeutic, when antigens were administered orally together with fully non toxic mutants of Escherichia coli heat-labile enterotoxin, as mucosal adjuvants. This experimental mouse model allows the study of the pathogenesis of Helicobacter pylori infection and the development of vaccines.

L32 ANSWER 6 OF 18 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:773428 HCAPLUS
DOCUMENT NUMBER: 128:60458
TITLE: Therapeutic intragastric vaccination against Helicobacter pylori in mice eradicates an otherwise chronic infection and confers protection against reinfection
AUTHOR(S): Ghiara, Paolo; Rossi, Michela; Marchetti, Marta; Di Tommaso, Annalisa; Vindigni, Carla; Ciampolini, Fabrizio; **Covacci, Antonello**; **Telford, John L.**; De Magistris, Maria Teresa; Pizza, Mariagrazia; **Rappuoli, Rino**; Del Giudice, Giuseppe
CORPORATE SOURCE: IRIS, Chiron Vaccines Immunobiological Research Institute Siena, University of Siena, Siena, 53100, Italy
SOURCE: Infection and Immunity (1997), 65(12), 4996-5002
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Chronic infection of the gastroduodenal mucosae by the gram-neg. spiral bacterium Helicobacter pylori is responsible for chronic active gastritis, peptic ulcers, and gastric cancers such as adenocarcinoma and low-grade gastric B-cell lymphoma. The success of eradication by antibiotic therapy is being rapidly hampered by the increasing occurrence of antibiotic-resistant strains. An attractive alternative approach to combat this infection is represented by the therapeutic use of vaccines. In the present work, we have exploited the mouse model of persistent infection by

mouse-adapted H. pylori strains that we have developed to assess the feasibility of the therapeutic use of vaccines against infection. We report that an otherwise chronic H. pylori infection in mice can be successfully eradicated by intragastric vaccination with H. pylori antigens such as **recombinant** VacA and CagA, which were administered together with a genetically detoxified mutant of the heat-labile enterotoxin of Escherichia coli (referred to as LTK63), in which the serine in position 63 was replaced by a lysine. Moreover, we show that therapeutic vaccination confers efficacious protection against reinfection. These results represent strong evidence of the feasibility of therapeutic use of VacA- or CagA-based vaccine formulations against H. pylori infection in an animal model and give substantial preclin. support to the application of this kind of approach in human clin. trials.

L32 ANSWER 7 OF 18 MEDLINE
ACCESSION NUMBER: 1998087269 MEDLINE
DOCUMENT NUMBER: 98087269 PubMed ID: 9427397
TITLE: Helicobacter pylori toxin VacA induces **vacuole** formation by acting in the cell cytosol.
AUTHOR: de Bernard M; Arico B; Papini E; Rizzuto R; Grandi G; **Rappuoli R**; Montecucco C
CORPORATE SOURCE: Centro CNR Biomembrane and Dipartimento di Scienze Biomediche Sperimentali dell'Universita di Padova, Italy.
SOURCE: MOLECULAR MICROBIOLOGY, (1997 Nov) 26 (4) 665-74. Journal code: 8712028. ISSN: 0950-382X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980226
Last Updated on STN: 19980226
Entered Medline: 19980219

AB Cells exposed to Helicobacter pylori toxin VacA develop large **vacuoles** that originate from massive swelling of membranous compartments of late stages of the endocytic pathway. To determine if the toxin is active from the cell cytosol, cells were either microinjected with toxin or transfected with plasmids encoding VacA. Both procedures cause formation of intracellular **vacuoles**. Cytosolic localization of the toxin was assessed by indirect immunofluorescence with specific antibodies and by expression of an active green fluorescence protein (GFP)-VacA chimera. **Vacuoles** induced by internally produced VacA are morphologically and functionally identical to those induced by externally added toxin. It is concluded that VacA is a toxin acting intracellularly by altering a cytosol-exposed target, possibly involved in the control of membrane trafficking.

L32 ANSWER 8 OF 18 HCAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
ACCESSION NUMBER: 1998:419489 HCAPLUS
DOCUMENT NUMBER: 129:187685
TITLE: The inhibition of cell proliferation by Helicobacter pylori products
AUTHOR(S): Chmiela, M.; **Covacci, A.**; Waldstrom, T.; Rudnicka, W.

CORPORATE SOURCE: Department of Infectious Biology, University of Lodz, Lodz, Pol.
SOURCE: Zentralblatt fuer Bakteriologie, Supplement (1997), 29(Bacterial Protein Toxins), 214-215
CODEN: ZBASE2; ISSN: 0941-018X
PUBLISHER: Gustav Fischer Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB H. pylori infections progress in spite of specific immune response. This suggests that bacterial factors may inhibit the protective immunol. reactions of the host. Previously it was shown that somatic fraction of H. pylori inhibited the response of T cells to PHA. Bacterial LPS as a possible cause of the inhibitory effect was excluded. Somatic fractions for the strains differing by **vacuolating cytotoxin** activity demonstrated similar inhibitory effect towards T cells. The CagA protein was considered by the authors as one of bacterial agents which could be responsible partly for the paralyzing effect of bacterial somatic fractions. In the present study, **recombinant** CagA inhibited the PHA-induced response of T cells but also proliferation of THP-1 monocytes grown in the medium with GM-CSF. The inhibition of cell functions by H. pylori products may prevent the development of antimicrobial cellular immunity.

L32 ANSWER 9 OF 18 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 96029747 MEDLINE
DOCUMENT NUMBER: 96029747 PubMed ID: 7591088
TITLE: Helicobacter pylori **cytotoxin**: importance of native conformation for induction of neutralizing antibodies.
AUTHOR: Manetti R; Massari P; Burroni D; de Bernard M; Marchini A; Olivieri R; Papini E; Montecucco C; **Rappuoli R; Telford J L**
CORPORATE SOURCE: IRIS, Chiron-Biocine Immunobiological Research Institute Siena, Italy.
SOURCE: INFECTION AND IMMUNITY, (1995 Nov) 63 (11) 4476-80.
Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951130

AB We have attempted to express the Helicobacter pylori **vacuolating cytotoxin** in Escherichia coli. Although the 95-kDa **VacA** polypeptide was expressed abundantly, it completely lacked any biological activity. In addition, this material failed to induce neutralizing antibodies after immunization of rabbits. In contrast, highly purified high-molecular-mass **cytotoxin** from the supernatant of H. pylori cultures was active in a HeLa cell assay and effectively induced a neutralizing response in rabbits. Neutralizing sera were shown to contain a high proportion of antibodies which recognized conformational epitopes found only on the native toxin. The data indicate that toxin-neutralizing epitopes are conformational and that potential vaccines based on the **cytotoxin** may benefit

from the use of the intact molecule.

L32 ANSWER 10 OF 18 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 96163481 MEDLINE
DOCUMENT NUMBER: 96163481 PubMed ID: 8575456
TITLE: Lipid interaction of the 37-kDa and 58-kDa fragments of the Helicobacter pylori **cytotoxin**.
AUTHOR: Moll G; Papini E; Colonna R; Burroni D; **Telford J; Rappuoli R**; Montecucco C
CORPORATE SOURCE: Centre CNR Biomembrane, Universita di Padova, Italy.
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1995 Dec 15) 234 (3) 947-52.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960321
Last Updated on STN: 19980206
Entered Medline: 19960311

AB Helicobacter pylori **cytotoxin vacA** (95 kDa) causes a **vacuolar** degeneration of epithelial cells. There is evidence that this protein toxin acts inside cells, and hence has to cross a cell membrane. This **cytotoxin** is frequently obtained as two fragments of 58 kDa (p58) and 37 kDa (p37) and it is available only in minute amounts. Here, its membrane interaction was studied with the two fragments, produced in Escherichia coli. Light scattering and energy transfer experiments show that p37 and p58 cause aggregation and fusion of small unilamellar lipid vesicles; only a reversible aggregation is induced at neutral pH, whereas at acid pH fusion also takes place. p58, but not p37, causes potassium efflux from liposomes and this occurs only at acid pH. Hydrophobic photolabelling with photoactivatable phosphatidylcholines inserted into liposomes shows that both fragments are labelled at neutral pH. The amount of labelling of the two fragments is much higher at acid pH, consistent with a further penetration into the hydrophobic core of the lipid bilayer. Tryptophan fluorescence measurements indicate that the two fragments undergo a pH-driven conformational change. These data are consistent with **cytotoxin** entry in the cell cytosol via an intracellular acidic compartment.

L32 ANSWER 11 OF 18 HCAPLUS COPYRIGHT 2002 ACS DUPLICATE 6
ACCESSION NUMBER: 1996:641643 HCAPLUS
DOCUMENT NUMBER: 125:325670
TITLE: Immunogenicity of purified and **recombinant** antigens of Helicobacter pylori in the mouse
AUTHOR(S): Odera, G.; Burroni, D.; **Bugnoli, M.**; Ghiara, P.
CORPORATE SOURCE: Biocine SpA, Siena, 53100, Italy
SOURCE: Mikrooekologie und Therapie (1995), 25(Beitraege zum XIX. Internationalen Kongress fuer Mikrobielle Oekologie und Krankheiten, 1994), 139-143
CODEN: MITHE4; ISSN: 0720-0536
PUBLISHER: Institut fuer Mikrooekologie
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Mice were orally and peranterally immunized with 94 kDa **cytotoxin** (**VacA**) and urease from H. pylori. Both VacA and urease were highly immunogenic when injected parenterally. Serum IgG to urease A and urease B were present in mice immunized with purified urease s.c. Neither antigen induced an antibody response when administered orally. Neither oral or parenteral immunization protected from gastric damage after oral challenge with cytotoxin-producing H. pylori. Oral immunization with ureas plus heat-labile enterotoxin prevented H. pylori colonization after oral challenge with a suspension of H. pylori.

L32 ANSWER 12 OF 18 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC. DUPLICATE 7

ACCESSION NUMBER: 1994:325647 BIOSIS
DOCUMENT NUMBER: PREV199497338647
TITLE: Virulence determinants in Helicobacter pylori infection.
AUTHOR(S): **Covacci, A. (1)**; Censini, S. (1); **Telford, J. L. (1)**; **Bugnoli, M. (1)** ; Burroni, D. (1); Dell'orco, M.; Ghiara, P. (1); Xiang, Z. (1); **Macchia, G. (1)**; Papini, E.; Montecucco, C.; **Rappuoli, R. (1)**
CORPORATE SOURCE: (1) Immunobiol. Res. Inst. Siena, Via Fiorentina 1, 53100 Siena Italy
SOURCE: Freer, J. [Editor]; Aitken, R. [Editor]; Alouf, J. E. [Editor]; Boulnois, G. [Editor]. FEMS Symposium, (1994) No. 73, pp. 43-50. FEMS Symposium; Bacterial protein toxins.
Publisher: Gustav Fischer Verlag Wollgrasweg 49, D-7000 Stuttgart, Germany.
Meeting Info.: Sixth European Workshop Stirling, Scotland, UK June 27-July 2, 1993
ISSN: 0163-9188. ISBN: 3-437-11535-9, 1-56081-385-7.
DOCUMENT TYPE: Book; Conference
LANGUAGE: English

L32 ANSWER 13 OF 18 HCAPLUS COPYRIGHT 2002 ACS DUPLICATE 8

ACCESSION NUMBER: 1994:2256 HCAPLUS
DOCUMENT NUMBER: 120:2256
TITLE: Helicobacter pylori proteins useful for vaccines and diagnostics
INVENTOR(S): **Covacci, Antonello; Bugnoli, Massimo; Telford, John; Macchia, Giovanni; Rappuoli, Rino**
PATENT ASSIGNEE(S): Biocine Sclavo S.p.A., Italy
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9318150	A1	19930916	WO 1993-EP472	19930302

W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP,

KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG

AU 9336300	A1	19931005	AU 1993-36300	19930302
EP 643770	A1	19950322	EP 1993-905285	19930302
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07504565	T2	19950525	JP 1993-515309	19930302
EP 967279	A1	19991229	EP 1999-202698	19930302
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
JP 2000333686	A2	20001205	JP 2000-126696	19930302
JP 2000350591	A2	20001219	JP 2000-126695	19930302
US 6077706	A	20000620	US 1995-470260	19950606
US 6130059	A	20001010	US 1995-466662	19950606

PRIORITY APPLN. INFO.:	IT 1992-FI52	A	19920302
	WO 1993-EP158	A	19930125
	EP 1993-905285	A3	19930302
	JP 1993-515309	A	19930302
	WO 1993-EP472	A	19930302
	US 1994-256848	B3	19941021

AB The H. pylori genes for cytotoxin, CAI (cytotoxin-assocd. immunodominant) antigen, and heat-shock protein (of the hsp60 family) are cloned and sequenced. The nucleic acids and proteins may be used for diagnosis and the proteins for vaccination against H. pylori. The cytotoxin, or CT antigen, gene encoded a 140 kDa protein precursor of a 100 kDa protein with urease-independent vaculolating activity. The CAI antigen gene was absent in noncytotoxic H. pylori strains. The heterogeneity of the CAI antigen appeared to be due to internal duplications in the gene: strain G39 was found to have two identical repeats of a 102 bp sequence within the gene. The heat-shock protein gene was expressed in all H. pylori strains tested, both cytotoxic and noncytotoxic. Most sera from patients infected with H. pylori and exhibiting gastritis and ulcers contained antibodies to the hsp, but the degree of recognition varied greatly among the patients and the antibody levels did not show any obvious correlation with the type of disease.

L32 ANSWER 14 OF 18 HCAPLUS COPYRIGHT 2002 ACS DUPLICATE 9

ACCESSION NUMBER:	1993:667824 HCAPLUS
DOCUMENT NUMBER:	119:267824
TITLE:	Molecular characterization of the 128-kDa immunodominant antigen of Helicobacter pylori associated with cytotoxicity and duodenal ulcer
AUTHOR(S):	**Covacci, Antonello**; Censini, Stefano; **Bugnoli, Massimo**; Petracca, Roberto; Burroni, Daniela; **Macchia, Giovanni**; Massone, Annalisa; Papini, Emanuele; Xiang, Xhaoying; et al.
CORPORATE SOURCE:	Immunobiol. Res. Inst. Siena, Siena, 53100, Italy
SOURCE:	Proc. Natl. Acad. Sci. U. S. A. (1993), 90(12), 5791-5 CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Helicobacter pylori has been assocd. with gastritis, peptic ulcer, and gastric adenocarcinoma. The authors report the nucleotide sequence and expression of an immunodominant antigen of H. pylori and the immune response to the antigen during disease. The antigen, named CagA (**cytotoxin**-assocd. gene A), is a hydrophilic, surface-exposed protein of 128 kDa produced by most clin. isolates. The size of the cagA gene and its protein varies in different strains by a mechanism that involves duplication of regions within the gene. Clin. isolates that do not produce the antigen do not have the gene and are unable to produce an active **vacuolating cytotoxin**. An ELISA to detect the immune response against a **recombinant** fragment of this protein detects 75.3% of patients with gastroduodenal diseases and 100% of patients with duodenal ulcer ($P < 0.0005$), suggesting that only bacteria harboring this protein are assocd. with disease.

L32 ANSWER 15 OF 18 HCAPLUS COPYRIGHT 2002 ACS DUPLICATE 10
ACCESSION NUMBER: 1994:6614 HCAPLUS
DOCUMENT NUMBER: 120:6614
TITLE: The Hsp60 protein of Helicobacter pylori: structure and immune response in patients with gastroduodenal diseases
AUTHOR(S): **Macchia, Giovanni**; Massone, Annalisa; Burroni, Daniela; Covacci, Antonello; Censini, Stefano; **Rappuoli, Rino**
CORPORATE SOURCE: IRIS Immunobiol. Res. Inst. Siena, Siena, I-53100, Italy
SOURCE: Mol. Microbiol. (1993), 9(3), 645-52
CODEN: MOMIEE; ISSN: 0950-382X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Helicobacter pylori is a human pathogen that has been assocd. with gastritis, peptic ulcer and gastric carcinoma. The role of the direct action of H. pylori virulence factors and of the induction of autoreactive immunity in the development of chronic gastritis has not been clarified yet. Here the authors report the cloning and mol. characterization of a gene of H. pylori coding for a protein of 58 kDa, recognized by sera of patients affected by H. pylori-induced gastroduodenal diseases. This antigen is present in all the H. pylori strains tested and it belongs to the Hsp60 family of heat-shock proteins, with high homol. with other bacterial and eukaryotic proteins of the same family. This class of homologous proteins has been implicated in the induction of autoimmune disorders in different systems. The presence in infected patients of anti-H. pylori Hsp60 antibodies, potentially cross-reacting with the human homolog, and cross-reactivity between human Hsp60 and a rabbit antiserum against H. pylori Hsp60 suggest that a role of this protein in gastroduodenal diseases is possible.

L32 ANSWER 16 OF 18 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93313061 EMBASE
DOCUMENT NUMBER: 1993313061
TITLE: Molecular analysis of the Helicobacter pylori **cytotoxin** gene.
AUTHOR: **Telford J.L.**; Dell'Orco M.; Burroni D.; Comanducci M.; **Bugnoli M.**; Figura N.; **Covacci A.**; **Rappuoli R.**
CORPORATE SOURCE: Immunology Research Institute Siena, Via Fiorentina

1,53100 Siena, Italy
SOURCE: European Journal of Gastroenterology and Hepatology, (1993) 5/SUPPL. 2 (S22-S24).
ISSN: 0954-691X CODEN: EJGHES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objective: To assess the contribution of the **vacuolating cytotoxin** to Helicobacter pylori virulence. Design: Approximately 50% of clinical isolates of H. pylori produce a potent **vacuolating cytotoxin** and a **cytotoxin** -associated protein with a molecular weight of 128 000 (CagA). A molecular genetic analysis of **cytotoxin**-positive and -negative strains was performed to clarify the effects of this **cytotoxin** in H. pylori virulence. Methods: We used the polymerase chain reaction and molecular cloning to obtain the gene coding for the **cytotoxin**. **Cytotoxin**-positive and -negative strains of H. pylori were analysed by DNA hybridization and the use of antisera raised against the **recombinant cytotoxin**. Results: We cloned the entire gene coding for the **cytotoxin** and raised antisera against the gene product. This gene proved to be unrelated to the gene coding for the **cytotoxin**-associated protein (cagA gene). The protein was not produced by **cytotoxin**-negative strains of H. pylori, although cagA gene sequences were present in the genome. Conclusions: Although the cagA gene was absent in **cytotoxin** -negative H. pylori strains, the **cytotoxin** gene was present, but not expressed, suggesting that the cagA gene may regulate cytotoxicity.

L32 ANSWER 17 OF 18 JAPIO COPYRIGHT 2002 JPO

ACCESSION NUMBER: 2000-350591 JAPIO
TITLE: VACCINE AND HELICOBACTER PYLORI PROTEIN USEFUL IN DIAGNOSIS
INVENTOR: **COVACCI ANTONELLO; BUGNOLI MASSIMO; TELFORD JOHN; MACCHIA GIOVANNI; RAPPUOLI RINO**
PATENT ASSIGNEE(S): CHIRON SPA
PATENT INFORMATION:

PATENT NO	KIND	DATE	ERA	MAIN IPC
JP 2000350591	A	20001219	Heisei	C12N015-09

APPLICATION INFORMATION
STN FORMAT: JP 1993-126695 19930302
ORIGINAL: JP2000126695 Heisei
PRIORITY APPLN. INFO.: IT 1992-FI52 19920302
PRIORITY APPLN. INFO.: WO 1993-EP158 19930125
SOURCE: PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 2000
AN 2000-350591 JAPIO
AB PROBLEM TO BE SOLVED: To obtain a novel Helicobacter pylori protein which possesses a specific sequence containing a specific number of successive amino acids, can be linked with an antibody against Helicobacter pylori and is useful in the diagnosis or prophylaxis of

the above bacterial infection and as a vaccine for treatment.
SOLUTION: This Helicobacter pylori protein is a novel recombinant polypeptide which comprises a sequence containing at least 8 successive amino acids and is useful in the diagnosis or prophylaxis of the above bacterial infection and as a vaccine for treatment. The sequence containing at least 8 successive amino acids includes at least a part which can be linked with an antibody against Helicobacter pylori in this sequence consisting of at least 8 successive amino acids or in this polypeptide and is obtained from the amino acid sequence of the formula. This recombinant polypeptide is obtained by preparing the above bacteria-derived DNA library, screening out this library by a partial sequence and expressing the resultant gene.

L32 ANSWER 18 OF 18 JAPIO
ACCESSION NUMBER: 2000-333686 JAPIO
TITLE: VACCINE AND HELICOBACTER PYLORI PROTEIN USEFUL FOR DIAGNOSIS
INVENTOR: **COVACCI ANTONELLO; BUGNOLI MASSIMO; TELFORD JOHN; MACCHIA GIOVANNI; RAPPUOLI RINO**
PATENT ASSIGNEE(S): CHIRON SPA
PATENT INFORMATION:

PATENT NO	KIND	DATE	ERA	MAIN IPC
JP 2000333686	A	20001205	Heisei	C12N015-09

APPLICATION INFORMATION
STN FORMAT: JP 1993-126696 19930302
ORIGINAL: JP2000126696 Heisei
PRIORITY APPLN. INFO.: IT 1992-FI52 19920302
PRIORITY APPLN. INFO.: WO 1993-EP158 19930125
SOURCE: PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 2000
AN 2000-333686 JAPIO
AB PROBLEM TO BE SOLVED: To obtain a new recombinant polypeptide having a specific amino acid sequence, consisting of an antigenic protein of Helicobacter pylori, having immunogenicity and useful for a vaccine for the treatment, the diagnosis and the like of infection of the above bacterium.
SOLUTION: This recombinant polypeptide having immunogenicity, and exhibiting no function or substantially a low function as a toxin has the following characteristics: a new recombinant polypeptide containing a continuous sequence of at least 8 amino acids; the continuous sequence of at least 8 amino acids contains at least one site; the site can be bound to an antibody against Helicobacter pylori both in the sequence consisting of the continuous sequence of at least 8 amino acids and in the polypeptide; the continuous sequence of at least 8 amino acids is obtained from the amino acid sequence of the formula; and this polypeptide is useful for a vaccine, the diagnosis or the like of the infection of the above bacterium.

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Set Items Description
S1 763 (CT OR CYTOTOXIN? ? OR CYTO(W)TOXIN? ?)(5N)VACUOL? - key terms
S2 73 S1 AND RECOMBINAN?

S5 416 (VACA OR VAC(W)A)(S)(CYTOTOXIN? ? OR CYTO(W)TOXIN? ?)
S6 47 S5 AND RECOMBINAN?
S7 47 S6 AND (HP OR PYLORI)
S8 85 S2 OR S7
S9 42 RD (unique items)

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>>>No matching display code(s) found in file(s): 65, 113

9/3,AB/1 (Item 1 from file: 35)
DIALOG(R)File 35:Dissertation Abs Online
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01774080 AADAAI9982192
Probing the intracellular structure and function relationships of the Helicobacter *pylori"** vacuolating toxin
Author: Ye, Dan
Degree: Ph.D.
Year: 2000
Corporate Source/Institution: University of Houston (0087)
Source: VOLUME 61/08-B OF DISSERTATION ABSTRACTS INTERNATIONAL.
PAGE 4012. 122 PAGES
ISBN: 0-599-88698-6

Persistent <italic>Helicobacter *pylori"**</italic> infections can progress to peptic ulcer disease and stomach cancer in humans. Many <italic>H. *pylori"** </italic> strains secrete a *cytotoxin"** (*VacA"**)

that is an important virulence factor in the pathogenesis of this organism. *VacA"** causes perturbations in host cell intracellular membrane trafficking resulting in the formation of large vacuoles leading ultimately to erosion of the gastric epithelial membrane that proceeds ulcer development. However, the molecular mechanism by which *VacA"** induces vacuolation and intoxicates target cells is not clear. Elucidation of the fundamental intoxication mechanism is complicated because *VacA"** exhibits properties of the two major classes of bacterial toxins, those that act intracellularly from the host cell cytosol (AB toxins), and those that act directly from the plasma membrane (pore-forming toxins). To begin understanding the cellular modulatory effects of *VacA"**, we have designed approaches for testing the hypothesis that *VacA"** intoxicates cells as an intracellular-acting AB toxin. We have developed a transient transfection system to begin defining *VacA"** intracellular structure-function relationships. We identified a minimal intracellular vacuolating domain of *VacA"**, which supports the AB toxin model of cellular intoxication. Moreover, this finding serves as a springboard for future studies to identify the *VacA"** biochemical activity and intracellular target. We also discovered the first two point mutations of *VacA"** that totally abolish the toxin's intracellular activity. In addition to establishing the importance of the *VacA"** amino-terminus to toxin function, these inactive forms of *VacA"** are potential candidates for *recombinant"** vaccine development targeting <italic> H. *pylori"**</italic>-mediated diseases. Finally, we have designed approaches to reveal that *VacA"** functions intracellularly by assembling into higher-ordered species. Interestingly, these results do not support the overall hypothesis of this dissertation. We propose that *VacA"** may intoxicate mammalian cells as a “hybrid toxin” by acting from the cytosol as an oligomeric toxin, representing a novel model for bacterial toxins.

9/3,AB/2 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

15699179 PASCAL No.: 02-0407669
An antibody to VacA of Helicobacter *pylori"** in cerebrospinal fluid from patients with Guillain-Barre syndrome
CHIBA S; SUGIYAMA T; YONEKURA K; TANAKA S; MATSUMOTO H; FUJII N; EBISU S; SEKIGUCHI K
Department of Neurology, School of Medicine, Sapporo Medical University, Sapporo, Japan; Department of Gastroenterology, Hokkaido University Graduate School of Medicine, Sapporo, Japan; Department of Microbiology, School of Medicine, Sapporo Medical University, Japan; Higeta Shoyu Co Ltd, Chiba, Japan; Institute of Immunology, Tochigi, Japan
Journal: Journal of neurology, neurosurgery and psychiatry, 2002, 73 (1) 76-78
Language: English
Objective: To detect antibodies to *recombinant"** *vacuolating"** *cytotoxin"** (r-*VacA"**) of Helicobacter *pylori"** in cerebro-spinal fluid (CSF) from patients with Guillain-Barre syndrome (GBS). Methods: CSF samples from 13 patients with GBS (electrophysiologically classified as eight acute inflammatory demyelinating polyradiculoneuropathy (AIDP), four acute motor axonal neuropathy (AMAN), and one unexcitable nerve conduction) and eight disease control patients were studied. The r-*VacA"** protein was separated by SDS/PAGE, and Western blot analysis was carried out. Results: Six of the 13 patients with GBS had a specific IgG antibody to *VacA"** of H *pylori"**, which was confirmed by absorption experiments using r-

*VacA"**. Every patient with positive CSF anti-r-*VacA"** IgG had AIDP. Conclusion: The sequence homology previously found between *VacA"** and human (Na SUP + +K SUP +)-ATPase A subunit suggests that antibodies to *VacA"** involve ion channels in abaxonal Schwann cell plasmalemma resulting in demyelination in some patients with GBS.

9/3,AB/3 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal

15618699 PASCAL No.: 02-0322943
*Vacuolating"** *cytotoxin"** of Helicobacter *pylori"** induces apoptosis in the human gastric epithelial cell line AGS
KUCK Dirk; KOLMERER Bernhard; IKING-KONERT Christof; KRAMMER Peter H; STREMMEL Wolfgang; RUDI Jochen
Department of Medicine, University of Heidelberg, 69115 Heidelberg, Germany; European Molecular Biology Laboratory, 69012 Heidelberg, Germany; German Cancer Research Center, 69120 Heidelberg, Germany
Journal: Infection and immunity, 2001, 69 (8) 5080-5087
Language: English
Helicobacter *pylori"** induces cell death by apoptosis. However, the apoptosis-inducing factor is still unknown. The virulence factor *vacuolating"** *cytotoxin"** A (*VacA"**) is a potential candidate, and thus its role in apoptosis induction was investigated in the human gastric epithelial cell line AGS. The supernatant from the *vacA"** wild-type strain P12 was able to induce apoptotic cell death, whereas the supernatant from its isogenic mutant strain P14 could not. That *VacA"** was indeed the apoptosis-inducing factor was demonstrated further by substantial reduction of apoptosis upon treatment of AGS cells with a supernatant specifically depleted of native *VacA"**. Furthermore, a *recombinant"** *VacA"** produced in Escherichia coli was also able to induce apoptosis in AGS cells but failed to induce cellular vacuolation. These findings demonstrate that the vacuolating cytototoxin of H. *pylori"** is a bacterial factor capable of inducing apoptosis in gastric epithelial cells.

9/3,AB/4 (Item 3 from file: 144)
DIALOG(R)File 144:Pascal

15116489 PASCAL No.: 01-0277320
Helicobacter *pylori"** *vacuolating"** *cytotoxin"** binding to a putative cell surface receptor, heparan sulfate, studied by surface plasmon resonance
Pathogenesis and host response in "Helicobacter" infections
UTT Meeme; DANIELSSON Bengt; WADSTROEM Torkel
ANDERSEN Leif Percival, ed
Department of Infectious Diseases and Medical Microbiology, Lund University, Soelvegatan 23, 223 62 Lund, Sweden; Department of Pure and Applied Biochemistry, Lund University. Box 124, 221 00 Lund, Sweden
Department of Clinical Microbiology 7806, National University Hospital, Righospitalet, Tagensvej 20, 2200 Copenhagen, Denmark
International Workshop on Pathogenesis and Host Response, 4 (Helsingoer

DNK) 2000
Journal: FEMS immunology and medical microbiology, 2001, 30 (2) 109-113
Language: English
The Helicobacter *pylori"** *vacuolating"** *cytotoxin"** or *VacA"** toxin is a major virulence factor in H. *pylori"** infection and type B gastritis. We predicted heparin/heparan sulfate (H/HS) binding properties of the 58-kDa subunit of *VacA"** *cytotoxin"** using bioinformatics tools and showed this by surface plasmon resonance (SPR)-based biosensor studies. Putative H/HS binding peptides were synthesized and binding to HS was shown by SPR in the absence or presence of trifluoroethanol. We found that a *recombinant"** *cytotoxin"** *VacA"** polypeptide binds to surface-immobilized HS and propose that HS might be a receptor/co-receptor for H. *pylori"** *VacA"** *cytotoxin"**.

9/3,AB/5 (Item 4 from file: 144)
DIALOG(R)File 144:Pascal

14439863 PASCAL No.: 00-0098142
Serological response to Helicobacter *pylori"** *recombinant"** antigens in Chilean infected patients with duodenal ulcer, non-ulcer dyspepsia and gastric cancer
OPAZO P; MUELLER I; ROLLAN A; VALENZUELA P; YUDELEVICH A; GARCIA-DELAGUARDA R; URRA S; VENEGAS A
Unidad de Biologia Molecular, BIOS Chile IGSA, Santiago, Brazil; Departamento de Gastroenterologia, Facultad de Medicina, Pontificia Universidad Catolica de Chile, Santiago, Chile; Departamento de Genetica Molecular y Microbiologia, Facultad de Ciencias Biologicas, Pontificia Universidad Catolica de Chile, Santiago, Chile
Journal: APMIS. Acta pathologica, microbiologica et immunologica Scandinavica, 1999, 107 (12) 1069-1078
Language: English
We have previously cloned 10 Helicobacter *pylori"** antigen genes from a Chilean strain including: *cytotoxin"** *VacA"**, a truncated region of CagA (called A17), a species-specific protein (Ag26), urease subunits (UreA, UreB), a flagellin, (FlaB), heat shock proteins (HspA and HspB), an adhesin (HpaA) and a lipoprotein (Lpp20). Immunogenicity of these antigens was tested by immunoblot with sera of Chilean infected patients, revealing that HpaA, A17, HspB and *VacA"** were more frequently recognized (86%, 82%, 68% and 68%, respectively). According to the clinical condition, it was determined that Lpp20 was preferentially recognized by sera from non-ulcer dyspepsia patients (80%), A17 and *VacA"** by patients with duodenal ulcer (92% and 83% respectively), and HspB by patients with duodenal ulcer (83%) and gastric cancer (90%). An ELISA was developed with a purified mixture of A17 and *VacA"** antigens to test the different groups of patients. It was found that sera from duodenal ulcer patients showed higher values than those from non-ulcer dyspepsia patients, but this difference was not significant ($p<0.2$). Moreover, sera from gastric cancer patients showed values lower than those from non-ulcer dyspepsia patients ($p<0.019$). These results indicate that, in the Chilean population, antibodies raised against *VacA"** and A17 are not markers either for duodenal ulcer or for gastric cancer.

9/3,AB/6 (Item 5 from file: 144)
DIALOG(R)File 144:Pascal

14246563 PASCAL No.: 99-0449362
VacA seropositivity is not associated with the development of gastric cancer in a Japanese population
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Molecular Medicine Unit, St James's University Hospital, Leeds, United Kingdom; Department of Internal Medicine, Hirosaki University School of Medicine, Hirosaki, Japan; Department of Pathology, Hirosaki University School of Medicine, Hirosaki, Japan
Journal: European journal of gastroenterology & hepatology, 1999, 11 (8) 887-890
Language: English
Objectives Infection with Helicobacter pylor strains producing *vacuolating"** *cytotoxin"** (*VacA"**) is associated with enhanced gastric mucosal damage and the development of gastric mucosal atrophy. The aim of this study was to investigate whether *VacA"** seropositivity is associated with increasing risk of gastric cancer in Japanese populations which have much higher incidence of gastric cancer than Western populations. Methods Serum sample was collected from 81 patients with gastric cancer and 81 sex- and age-matched endoscopically evaluated control subjects. Histologically, 62 cancers were of the intestinal type and 76 were early gastric cancer. H. *pylori"** and *VacA"** IgG antibodies were assayed by Western blotting using Chiron Diagnostics' *Recombinant"** Immunoblot Assay (RIBA SUP a). Results *VacA"** seropositivity was 68% (55/81) in patients with gastric cancer and 70% (57/81) in controls. The odds ratio for the risk of gastric cancer in *VacA"** seropositives was 0.89 (95% CI 0.46-1.74). In H. *pylori"** seropositive patients and their control subjects (matched H. *pylori"**-positive controls), *VacA"** seropositivity was the same 80.6% (50/62). The odds ratio for the risk of gastric cancer in H. *pylori"**-positive patients if *VacA"** seropositive was 1.00 (95% Cl 0.41-2.44). The mean relative intensity of *VacA"** antibody titre was 3.01 +- 0.18 in the 55 *VacA"** seropositive cancer patients and 3.09 +- 0.17 in the 57 *VacA"** seropositive control subjects (difference not significant). Conclusion These results suggest that *VacA"** seropositivity is not associated with increasing risk of gastric cancer in Japanese populations.

9/3,AB/7 (Item 6 from file: 144)
DIALOG(R)File 144:Pascal

14235941 PASCAL No.: 99-0437835
Epidemiology of Helicobacter *pylori"** in chronic haemodialysis patients using the new RIBA SUP H. *pylori"** SIA
FABRIZI F; MARTIN P; DIXIT V; QUAN S; BREZINA M; ABBEY H; GEROSA S; KAUFMAN E; DINELLO R; POLITO A; GITNICK G
Division of Digestive Diseases, UCLA School of Medicine, Los Angeles, United States; Division of Nephrology and Dialysis, Lecco Hospital, Lecco, Italy; Chiron Corporation, CA, United States
Journal: Nephrology, dialysis, transplantation, 1999, 14 (8) 1929-1933
Language: English

Background. There are few data concerning the epidemiology of H. *pylori"** in patients on chronic haemodialysis (HD) treatment. These surveys concerned small populations and were made with ELISA technique. However, ELISA-based assays do not differentiate between strains of H. *pylori"** that are associated with ulcers. Recent literature reports that formation of ulcers correlates strongly with the expression of *cytotoxin"**-associated protein (CagA) and *vacuolating"** *cytotoxin"** (*VacA"**) of H. *pylori"**. Methods. A novel serological test (RIBA SUP H. *pylori"** strip immunoblot assay (SIA)) has been recently introduced, it uses the H. *pylori"** lysate (Lys) along with two additional purified *recombinant"** antigens derived from CagA and *VacA"** of H. *pylori"**. Aim. To study the epidemiology of H. *pylori"** using RIBA SUP H. *pylori"** SIA among chronic HD patients and blood donors as a control group. In addition, the activity of H. *pylori"** was analysed by immunoblot technique in a group of patients with documented ulcers and normal renal function. Results. The prevalence of antibody towards H. *pylori"** among HD patients, blood donors, and patients with documented ulcers was 56% (127/228), 53% (84/158), and 100% (21/21) respectively; the difference was significant (P=0.0001). The frequency of anti-H. *pylori"** -positive individuals was significantly higher in patients with documented ulcers than HD patients and blood donors, 21/21 (100%) vs 211/386 (55%), P=0.0001. The frequency of antibody to H. *pylori"** in the HD population was significantly associated with race (P= 0.005); no relationship between anti-H. *pylori"** antibody and numerous demographic, biochemical, and clinical features of patients was seen. The frequency of antibodies against virulent strains of H. *pylori"** in HD patients and blood donors with H. *pylori"** was 60% (76/127) and 61% (51/84) respectively; it was 86% (18/21) among individuals with documented ulcers. No significant difference among these three groups occurred. Conclusions. The frequency of antibody towards H. *pylori"** by RIBA SUP H. *pylori"** SIA was high both in HD patients and blood donors; patients with documented ulcers and normal renal function had significantly higher frequency of anti-H. *pylori"** antibody. The anti-H. *pylori"** antibody rate among HD patients was strongly associated with race. The prevalence of antibody against virulent strains of H. *pylori"** did not change among HD patients and control groups. Studies in large cohorts of HD patients with documented peptic ulcer disease are in progress.

9/3,AB/8 (Item 7 from file: 144)
DIALOG(R)File 144:Pascal

13967934 PASCAL No.: 99-0150116
Helicobacter *pylori"** and type 1 diabetes mellitus in children
SALARDI S; CACCIARI E; MENEGATTI M; LANDI F; MAZZANTI L; STELLA F A; PIRAZZOLI P; VAIRA D
First Pediatric Clinic, University of Bologna, Bologna, Italy; 1st Medical Clinic, University of Bologna, Bologna, Italy
Journal: Journal of pediatric gastroenterology and nutrition, 1999, 28 (3) 307-309
Language: English
Background: Helicobacter *pylori"** is a recognized gastroduodenal pathogen and H. *pylori"** infection is one of the most common bacterial infections, usually acquired during childhood. However, diabetes mellitus is characterized by an increased susceptibility to infections. Methods: We

compared the prevalence of H. *pylori"** infection as well as *cytotoxin"** -associated gene A-CagA-and *vacuolating"** *cytotoxin"** gene A-*VacA"** -positivity in 103 children and adolescents with type I diabetes mellitus and in 236 nondiabetic children. We used a novel *Recombinant"** ImmunoBlot Assay-Strip (RIBA SIA) with individual band for whole H. *pylori"** lysate and *recombinant"** CagA and *VacA"**. Results: H. *pylori"**-positive subjects, both diabetics and controls, were significantly older than negative subjects. In the whole group of diabetic patients the prevalence of each of the three reactivities was higher than in control subjects, reaching significance only for lysate. Only diabetic patients over 12 years of age, with a longer disease duration, had a higher prevalence of positive cases, although not significantly so. Conclusions: In the first few years of disease, diabetic children do not differ from the nondiabetic population. Subsequently they show an H. *pylori"** seroprevalence tendentially higher than that of controls of the same age. Therefore. H. *pylori"** infection acquired in childhood and lasting several years, could be one of the causes of chronic atrophic gastritis, which is more frequent in longstanding diabetes mellitus.

9/3,AB/9 (Item 8 from file: 144)
DIALOG(R)File 144:Pascal

13466053 PASCAL No.: 98-0162734
Major virulence factors, VacA and CagA, are commonly positive in Helicobacter *pylori"** isolates in Japan
MAEDA S; OGURA K; YOSHIDA H; KANAI F; IKENOUE T; KATO N; SHIRATORI Y; OMATA M
Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan
Journal: Gut, 1998, 42 (3) 338-343
Language: English
Background-*VacA"** and CagA proteins have been reported to be major virulence factors of Helicobacter *pylori"**. However, antibodies against these proteins are frequently found in the sera of Japanese patients regardless of their gastroduodenal status. Aim-To evaluate the expression of *VacA"** and CagA proteins by H *pylori"** strains isolated in Japan. Methods-By using specific antibodies raised against *recombinant"** *VacA"** and CagA proteins, the expression of *VacA"** and CagA was evaluated in 68 H *pylori"** strains isolated from Japanese patients; a vacuolating assay and genotyping of the *vacA"** gene were also used in the evaluation. The results were analysed in relation to the gastroduodenal diseases of the hosts. Results-*VacA"** and CagA proteins were expressed in 59/68 (87%) and in 61/68 (90%) isolates respectively. The vacuolating assay was positive in 57168 (84%) isolates, indicating that most immunologically *VacA"** positive strains produced active *cytotoxin"**. The prevalence of infection with strains expressing CagA and positive for vacuolating activity (Type I) was very high, 54/68 (79%), irrespective of the gastroduodenal status of the host. Conclusion-Most H *pylori"** isolates in Japan are positive for *vacuolating"** *cytotoxin"** and CagA, and thus these virulence factors cannot be used as markers to discern the risk of developing serious gastroduodenal pathologies in the hosts. However, the high prevalence of infection with strains positive for *vacuolating"** *cytotoxin"** and CagA may contribute to the characteristics of H *pylori"** infection in Japan.

9/3,AB/10 (Item 9 from file: 144)
DIALOG(R)File 144:Pascal

13253588 PASCAL No.: 97-0523789
High prevalence of cytotoxin positive Helicobacter *pylori"** in patients unrelated to the presence of peptic ulcers in Japan
OGURA K; KANAI F; MAEDA S; YOSHIDA H; OGURA M; LAN K H; HIROTA K; KAWABE T; SHIRATORI Y; OMATA M
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Journal: Gut, 1997, 41 (4) 463-468
Language: English
Background-It has been reported that infection with *vacuolating"** *cytotoxin"** positive Helicobacter *pylori"** strains is associated with gastroduodenal disease in Western countries. Aims-To evaluate the prevalence of *cytotoxin"** producing strains among patients with H *pylori"** infection in relation to gastrointestinal diseases in Japan. Patients-Ninety seven patients undergoing endoscopy. Methods-A Western blot assay was conducted to detect serum antibodies against the *cytotoxin"** using *recombinant"** *cytotoxin"** (*VacA"** protein) as an antigen. To obtain a purified *recombinant"** *cytotoxin"**, the *vacA"** gene (2233 nucleotides) was cloned into an expression vector to produce the protein (744 amino acids), which was expressed in Escherichia coli. Results-Serum IgG antibodies to the *cytotoxin"** were present in 85%, 95%, 95%, and 100% of infected patients with gastric ulcer (n=26), duodenal ulcer (n=21), chronic gastritis (n=19), and endoscopically normal mucosa (n=14), respectively. Conclusion-The western blot method using *recombinant"** *VacA"** protein is simple and useful for detecting antibody to *vacuolating"** *cytotoxin"**. This method showed antibodies against *cytotoxin"** were highly prevalent, even in subjects with endoscopically normal mucosa in Japan, indicating that the *cytotoxin"** may not be an independent cause of gastrointestinal diseases induced by H *pylori"** infection.

9/3,AB/11 (Item 10 from file: 144)
DIALOG(R)File 144:Pascal

12731031 PASCAL No.: 96-0439649
Binding and internalization of the Helicobacter *pylori"** *vacuolating"** *cytotoxin"** by epithelial cells
GARNER J A; COVER T L
Division of Infectious Diseases, Department of Medicine, Vanderbilt University School of Medicine, Nasvhille, Tennessee, United States; Veterans Administration Medical Center, Nasvhille, Tennessee, United States
Journal: Infection and immunity, 1996, 64 (10) 4197-4203
Language: English
Many Helicobacter *pylori"** strains produce a *cytotoxin"** (*VacA"**) that induces *vacuolation"** in epithelial cells. In this study, binding

and internalization of the *cytotoxin"** by HeLa or AGS (human gastric adenocarcinoma) cells were characterized by indirect fluorescence microscopy. Cells incubated with the *cytotoxin"** at 4 Degree C displayed a uniform fluorescent plasma membrane signal. Preincubation of the *cytotoxin"** with either rabbit antiserum to similar 90-kDa H. *pylori"** *VacA"** or sera from H. *pylori"**-infected persons inhibited its binding to cells and blocked its capacity to induce cytoplasmic vacuolation. *Recombinant"** *VacA"** fragments (similar 34 and similar 58 kDa), corresponding to two proteolytic cleavage products of similar 90-kDa *VacA"** , each bound to the plasma membrane of HeLa cells. Antiserum reactive with the similar 58-kDa *VacA"** fragment inhibited the binding of native H. *pylori"** *cytotoxin"** to cells and inhibited *cytotoxin"** activity, whereas antiserum to the similar 34-kDa fragment had no effect. When incubated with cells at 37 Degree C for >=3 h, the H. *pylori"** *cytotoxin"** localized intracellularly in a perinuclear location but did not localize within *cytotoxin"**-induced *vacuoles"**. When cells with previously bound *cytotoxin"** were incubated with anticytotoxin serum at 4 Degree C and then shifted to 37 Degree C, *vacuolation"** was completely inhibited. Bound *cytotoxin"** became inaccessible to the neutralizing effects of antiserum after 60 to 120 min of incubation with cells at 37 Degree C. These data suggest a model in which (i) *VacA"** binds to cells primarily via amino acid sequences in its 58-kDa fragment, (ii) *VacA"** internalization occurs slowly in a temperature-dependent process, and (iii) *VacA"** interacts with an intracellular target.

9/3,AB/12 (Item 1 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

13326862 References: 34
TITLE: Immune response to a 26-kDa protein, alkyl hydroperoxide reductase, in Helicobacter pylori-infected Mongolian gerbil model
AUTHOR(S): Yan J; Kumagai T; Ohnishi M; Ueno I; Ota H (REPRINT)
CORPORATE SOURCE: Shinshu Univ, Dept Med Technol, Asahi 3-1-1/Nagano 3908621//Japan/ (REPRINT); Shinshu Univ, Dept Lab Med, /Matsumoto/Nagano 390/Japan/; Shinshu Univ Hosp, Cent Clin Labs, /Matsumoto/Nagano/Japan/; Shinshu Univ, Dept Med Technol, /Matsumoto/Nagano 390/Japan/; Miyazaki Med Coll, Dept Microbiol, /Kiyatake//Japan/
PUBLICATION TYPE: JOURNAL
PUBLICATION: HELICOBACTER, 2001, V6, N4 (DEC), P274-282
GENUINE ARTICLE#: 503PL
PUBLISHER: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148 USA
ISSN: 1083-4389
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Background. The host immune response is thought to play an important role in the outcome of Helicobacter pylori infection. The successful development of the H. pylori-infected Mongolian gerbil model that mimics human disease has enabled study of the antibody response against H. pylori antigens.

Materials and Methods. Serurn samples from ulcer and carcinogenesis models of H. pylori-infected gerbils were used to screen for H. pylori antigens that cause a humoral immune response in the infected hosts. H. pylori alkyl hydroperoxide reductase (AhpC) is one such antigen on which we report here. The tsaA gone encoding AhpC was amplified by PCR from H.

pylori ATCC 43504 strain, cloned into pMAL(TM)-c2 expression vector and expressed in Escherichia coli. Maltose-binding protein fusion protein (MBP-AhpC) was purified by a MBP affinity column. Using purified *recombinant"** AhpC protein as an antigen, the antibody response and changes of antibody levels against AhpC in the gerbil models were studied by Western blotting and ELISA.

Results. Antibody against AhpC was negative in the early stages of infection, and became positive in the gerbils with the emergence of gastric diseases such as chronic active gastritis, gastric ulcer and gastric cancer. The antibody levels (ELISA) increased gradually over time and were higher in gerbils with gastric ulcer than that in gerbils without ulcers.

Conclusions. Use of the gerbil model that mimics human H. pylori infection is likely to provide insights into the role of H. pylori-specific antigens possibly related to the subsequent development of gastric diseases.

9/3,AB/13 (Item 2 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

13261360 References: 85
TITLE: Vaccination against Helicobacter pylori - an old companion of man
AUTHOR(S): Keller WCF (REPRINT); Michetti P
AUTHOR(S) E-MAIL: walther.keller@chuv.hospvd.ch
CORPORATE SOURCE: CHU Vaudois, Div Gastroenterol, /CH-1011 Lausanne//Switzerland/ (REPRINT); CHU Vaudois, Div Gastroenterol, /CH-1011 Lausanne//Switzerland/
PUBLICATION TYPE: JOURNAL
PUBLICATION: EXPERT OPINION ON BIOLOGICAL THERAPY, 2001, V1, N5 (SEP), P 795-802
GENUINE ARTICLE#: 493YA
PUBLISHER: ASHLEY PUBLICATIONS LTD, UNITEC HOUSE, 3RD FL, 2 ALBERT PLACE FINCHLEY CENTRAL, LONDON N3 1QB, ENGLAND
ISSN: 1471-2598
LANGUAGE: English DOCUMENT TYPE: REVIEW

ABSTRACT: Helicobacter pylori infection induces an important systemic and mucosal antibody response and a predominant Th1 cellular response. These immune responses, although powerful, fail to eliminate the infection. Studies in animals have shown that prophylactic and therapeutic immunisations are efficacious, although complete protective immunity has usually not been achieved. Initial human trials with *recombinant"** urease showed that a mucosal immune response can be obtained following immunisations, with a decrease in bacterial density, but successful immunisation is still awaited. Progress is being made in several areas of vaccine design. A human vaccine against H. pylori would be favourable in terms of health benefits and costs in developed and developing countries.

9/3,AB/14 (Item 3 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

13163397 References: 36
TITLE: Outer membrane targeting of passenger proteins by the

*vacuolating"** *cytotoxin"** autotransporter of Helicobacter *pylori"**
AUTHOR(S): Fischer W (REPRINT); Buhrdorf R; Gerland E; Haas R
AUTHOR(S) E-MAIL: schmitt@m3401.mpk.med.uni-muenchen.de
CORPORATE SOURCE: Univ Munich, Max Von Pettenkofer Inst Hyg & Med Microbiol, Pettenkoferstr 9A/D-80336 Munich//Germany/ (REPRINT); Univ Munich, Max Von Pettenkofer Inst Hyg & Med Microbiol, /D-80336 Munich//Germany/
PUBLICATION TYPE: JOURNAL
PUBLICATION: INFECTION AND IMMUNITY, 2001, V69, N11 (NOV), P6769-6775
GENUINE ARTICLE#: 485DX
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA
ISSN: 0019-9567
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Helicobacter *pylori"** produces a number of proteins associated with the outer membrane, including adhesins and the *vacuolating"** *cytotoxin"**. These proteins are supposed to integrate into the outer membrane by beta -barrel structures, characteristic of the family of autotransporter proteins. By using the SOMPES (shuttle vector-based outer membrane protein expression) system for outer membrane protein production, we were able to functionally express in H. *pylori"** the cholera toxin B subunit genetically fused to the C-terminal *VacA"** domain. We demonstrate that the fusion protein is translocated to the H. *pylori"** outer membrane and that the CtxB domain is exposed on the H. *pylori"** surface. Thus, we provide the first experimental evidence that the C-terminal beta -domain of *VacA"** can transport a foreign passenger protein to the H. *pylori"** surface and hence acts as a functional autotransporter.

9/3,AB/15 (Item 4 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

13114726 References: 49
TITLE: Two distinctive cell binding patterns by vacuolating toxin fused with glutathione S-transferase: one high-affinity m1-specific binding and the other lower-affinity binding for variant m forms
AUTHOR(S): Wang WC (REPRINT); Wang HJ; Kuo CH
AUTHOR(S) E-MAIL: lswwc@life.nthu.edu.tw
CORPORATE SOURCE: Natl Tsing Hua Univ, Dept Life Sci, /Hsinchu//Taiwan/ (REPRINT); Natl Tsing Hua Univ, Dept Life Sci, /Hsinchu//Taiwan/
PUBLICATION TYPE: JOURNAL
PUBLICATION: BIOCHEMISTRY, 2001, V40, N39 (OCT 2), P11887-11896
GENUINE ARTICLE#: 479HZ
PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA
ISSN: 0006-2960
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: The Helicobacter *pylori"** VacA causes large intracellular vacuoles in epithelial cells such as HeLa or RK13 cells. Two major VacA forms, m1 and m2, divergent in an similar to 300 amino acid segment within the cell binding domain P58, display distinct cell-type specificity. Sequence analysis of four vacA alleles showed that a in m1-like allele (61) and two m2 alleles (62 and v226) mainly differed in the midregion and that v225, a m1m2 chimera, was a natural double crossover from v226 and another allele. Each of these alleles was expressed as a soluble GST-VacA fusion

that did not form a large oligomer. The *recombinant"** VacA portion nevertheless assembled into higher ordered structures and possessed biological binding activity similar to that of the native VacA. A direct comparison of fusion-cell binding activity showed that m1 > m1m2 > m2 in HeLa cells, whereas there were more similar activities in RK13 cells. Vacuolating analyses of three forms revealed a positive correlation between cell binding activity and vacuolating activity. Moreover, the m1-type N-terminal half portion of the midregion was crucial for HeLa cell cytotoxicity. Kinetic, Scatchard, and inhibition analyses suggested the presence of at least two receptors: a m1-type specific high-affinity receptor (K-d = similar to5 nM) and a common VacA receptor interacting similarly with m1, m1m2, and m2 via a lower affinity (K-d = 45-67 nM). Expression of mainly the m1-type receptor on HeLa cells whereas both receptors on RK13 cells may account for distinct cell binding activity and therefore for cell-type specificity.

9/3,AB/16 (Item 5 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

12785968 References: 64
TITLE: Population genetics of Helicobacter pylori in the southern part of Switzerland analysed by sequencing of four housekeeping genes (atpD, glnA, scoB and recA), and by vacA, cagA, iceA and IS605 genotyping
AUTHOR(S): Solca NM; Bernasconi MV; Valsangiacomo C; Van Doorn LJ; Piffaretti JC (REPRINT)
AUTHOR(S) E-MAIL: jean-claude.piffaretti@ti.ch
CORPORATE SOURCE: Ist Cantonale Batteiosierol, Via Osped 6/CH-6904 Lugano//Switzerland/ (REPRINT); Ist Cantonale Batteiosierol, /CH-6904 Lugano//Switzerland/; Delft Diagnost Lab, /NL-2625 AD Delft//Netherlands/
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PUBLICATION: MICROBIOLOGY-SGM, 2001, V147, ,6 (JUN), P1693-1707
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PUBLISHER: SOC GENERAL MICROBIOLOGY, MARLBOROUGH HOUSE, BASINGSTOKE RD, SPENCERS WOODS, READING RG7 1AE, BERKS, ENGLAND
ISSN: 1350-0872
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: The population biology of 78 Helicobacter pylori strains (71 from Swiss Italian. 4 from East Asian and 3 from South African patients) was investigated by sequence analysis of four housekeeping genes: atpD, scoB, glnA and recA. The vacA genotype, the presence of cagA and IS605. the iceA allelic type. and the resistance to metronidazole. clarithromycin and amoxycillin were determined. A high percentage of DNA polymorphic sites (19.8% for atpD. 21.3% for scoB, 23.7% for glnA and 20.3% for recA) was found. The phylogenetic trees based on the nucleotide sequences of the four gene fragments showed different topologies and were incongruent. The virulence-associated markers were distributed over the dendrograms and no association was found with phylogenetic clusters or clinical manifestations (chronic gastritis, gastric or duodenal ulcer. MALT lymphoma). Moreover, the H ratios (calculated with the homoplasy test) ranged from 0.742 to 0.799. depending on the gene fragment examined. All these observations suggest that H. pylori exists as a *recombinant"** population. The clustering of the strains according to their geographical origin (USA/Europe. East Asia, South Africa) that has recently been demonstrated elsewhere could only be confirmed for the East Asian vacA sie strains. In contrast, the South African strains clustered together only in the atpD

tree. Presumably, recombination at the different loci has masked the evolutionary relationship among the strains.

9/3,AB/17 (Item 6 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

12598743 References: 45
TITLE: Assessment of Helicobacter pylori vacA and cagA genotypes and host serological response
AUTHOR(S): Figueiredo C; Quint W; Nouhan N; van den Munckhof H; Herbrink P; Scherpenisse J; de Boer W; Schneeberger P; Perez-Perez G; Blaser MJ; van Doorn LJ (REPRINT)
AUTHOR(S) E-MAIL: L.J.van.Doorn@ddl.nl
CORPORATE SOURCE: Delft Diagnost Lab, R de Graafweg 7/NL-2625 AD Delft//Netherlands/ (REPRINT); Delft Diagnost Lab, /NL-2625 AD Delft//Netherlands/; R De Graaf Hosp, /Delft//Netherlands/; Bernhoven Hosp, Dept Internal Med, /Oss//Netherlands/; Bosch Medicentrum, Dept Microbiol, /Den Bosch//Netherlands/; Univ Porto, IPATIMUP, /P-4100 Porto//Portugal/; Univ Porto, Fac Med, /P-4100 Porto//Portugal/; Vanderbilt Univ, Div Infect Dis, /Nashville//TN/; NYU, Dept Med, /New York//NY/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF CLINICAL MICROBIOLOGY, 2001, V39, N4 (APR), P 1339-1344
GENUINE ARTICLE#: 419JX
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA
ISSN: 0095-1137
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Helicobacter pylori strains can be distinguished by genotyping of virulence-associated genes, such as vacA and cagA. Because serological discrimination between strain types would reduce the need for endoscopy, 61 patients carrying H. pylori were studied by vacA and cagA genotyping of H. pylori in gastric biopsy specimens and by detection of specific serum antibodies. Serological responses to H. pylori were determined by Helicoblot (versions 2.0 and 2.1). Antibodies to CagA also were determined by a rapid anti-CagA assay (Pyloriset screen CagA) as well as by two noncommercially developed enzyme immunoassays, each using a *recombinant"** CagA protein. Assessment of performance of the Helicoblot assays indicated substantial interobserver variation, with kappa values between 0.20 and 0,93. There was no relationship between the serological profiles on the Helicoblot and the genotypes from the same patients, except for strong associations between the presence of anti-CagA and the cagA-positive and racA s1 H. pylori genotypes, Detection of anti-CagA by the five different assays varied considerably, with kappa values ranging from 0.21 to 0.78, Using the cagA genotype as the "gold standard," the sensitivity and specificity of the anti-CagA assays varied from 71.4 to 85.7% and from 54.2 to 100%, respectively. Thus, serological profiles of antibodies to H. pylori are heterogeneous and, with the exception of anti-CagA antibodies, show no relation to the H. pylori vacA and cagA genotypes, Detection of anti-CagA antibodies is strongly dependent on the test used.

9/3,AB/18 (Item 7 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

12572067 References: 111
TITLE: Virulence factors of Helicobacter pylori
AUTHOR(S): Dundon WG; de Bernard M; Montecucco C (REPRINT)
AUTHOR(S) E-MAIL: cesare@civ.bio.unipd.it
CORPORATE SOURCE: Univ Padua, Ctr Biomembrane, Via G Colombo 3/I-35121 Padua//Italy/ (REPRINT); Univ Padua, Ctr Biomembrane, /I-35121 Padua//Italy/; Univ Padua, Dipartimento Sci Biomed, /I-35121 Padua//Italy/
PUBLICATION TYPE: JOURNAL
PUBLICATION: INTERNATIONAL JOURNAL OF MEDICAL MICROBIOLOGY, 2001, V290, N8 (MAR), P647-658
GENUINE ARTICLE#: 417WB
PUBLISHER: URBAN & FISCHER VERLAG, BRANCH OFFICE JENA, P O BOX 100537, D-07705 JENA, GERMANY
ISSN: 1438-4221
LANGUAGE: English DOCUMENT TYPE: REVIEW

ABSTRACT: To date a number of virulence factors have been identified and characterised from the gastric pathogen Helicobacter pylori. The vacuolating toxin (VacA) is a major determinant of H. pylori-associated gastric disease. In non-polarised cells, VacA alters the endocytic pathway, resulting in the release of acid hydrolases and the reduction of both extracellular ligand degradation and antigen processing. The toxin forms trans-membrane anion-specific channels and reduces the transepithelial electrical resistance of polarized monolayers. Localization of the VacA channels in acidic intracellular compartments causes osmotic swelling which, together with membrane fusion, leads to vacuole formation. The neutrophil-activating protein of H. pylori (HP-NAP) induces the production of oxygen radicals in human neutrophils via a cascade of intracellular activation events which may contribute to the damage of the stomach mucosa. This protein has recently been shown to be an important antigen in the human immune response to H. pylori infection. In addition, mice vaccinated with *recombinant"** HP-NAP were protected against H. pylori challenge. H. pylori strains that are associated with severe tissue damage and inflammation possess the cag pathogenicity island that contains several genes encoding factors involved in the induction of proinflammatory cytokines/chemokines and of a type IV secretion system involved in the delivery of a highly immunogenic protein, CagA, into eukaryotic cells. Recent advances in our understanding of the involvement of VacA, HP-NAP and the CagA/Type IV secretion system in the H. pylori-associated disease process are discussed in this review.

9/3,AB/19 (Item 8 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

11732472 References: 26
TITLE: Mutational analysis of the Helicobacter *pylori"** vacuolating toxin amino terminus: Identification of amino acids essential for cellular vacuolation
AUTHOR(S): Ye D; Blanke SR (REPRINT)
AUTHOR(S) E-MAIL: sblanke@uh.edu
CORPORATE SOURCE: Univ Houston, Dept Biol & Biochem, 430 Houston Sci Ctr,3201 Cullen Blvd/Houston//TX/77204 (REPRINT); Univ Houston, Dept Biol & Biochem, /Houston//TX/77204

PUBLICATION TYPE: JOURNAL
PUBLICATION: INFECTION AND IMMUNITY, 2000, V68, N7 (JUL), P4354-4357
GENUINE ARTICLE#: 326AT
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA
ISSN: 0019-9567
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: The functional importance of the amino terminus of the Helicobacter *pylori"** *vacuolating"** *cytotoxin"** (*VacA"**) was investigated by analyzing the relative levels of vacuolation of HeLa cells transfected with plasmids encoding wild-type and mutant forms of the toxin. Notably, *VacA"**'s intracellular activity was found to be sensitive to small truncations and internal deletions at the toxin's amino terminus. Moreover, alanine scanning mutagenesis revealed the first *VacA"** point mutations (at proline 9 or glycine 14) that completely abolish the toxin's intracellular activity.

9/3,AB/20 (Item 9 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

11602172 References: 17
TITLE: *Recombinant"** CagA enzyme-linked immunosorbent assay and western immunoblot for the detection of serum antibodies to Helicobacter *pylori"**
AUTHOR(S): Donati M (REPRINT); Sambri V; Ranucci L; De Orsi D; Tucci A; Poli L; Cevenini R
AUTHOR(S) E-MAIL: Cevenini@almadns.unibo.it
CORPORATE SOURCE: Univ Bologna, Sez Microbiol DMCSS, /I-40138 Bologna//Italy/ (REPRINT); Univ Bologna, Sez Microbiol DMCSS, /I-40138 Bologna//Italy/; Univ Bologna, Dipartimento Med Interna & Gastroenterol, /Bologna//Italy/
PUBLICATION TYPE: JOURNAL
PUBLICATION: CLINICAL MICROBIOLOGY AND INFECTION, 2000, V6, N3 (MAR), P 164-166
GENUINE ARTICLE#: 311YU
PUBLISHER: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND
ISSN: 1198-743X
LANGUAGE: English DOCUMENT TYPE: ARTICLE

9/3,AB/21 (Item 10 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

11544582 References: 30
TITLE: Genetic organization and heterogeneity of the iceA locus of Helicobacter *pylori"**
AUTHOR(S): Figueiredo C; Quint WGV; Sanna R; Sablon E; Donahue JP; Xu Q; Miller GG; Peek RM; Blaser MJ; van Doorn LJ (REPRINT)
AUTHOR(S) E-MAIL: L.J.van.Doorn@ddl.nl
CORPORATE SOURCE: Delft Diagnost Lab, R Graafweg 7/NL-3525 AD Delft//Netherlands/ (REPRINT); Delft Diagnost Lab, /NL-3525 AD Delft//Netherlands/; Univ Porto, IPATIMUP, /P-4100 Porto//Portugal/; Univ Porto, Fac Med, /P-4100 Porto//Portugal/; Innogenet NV, /Ghent//Belgium/;

Vanderbilt Univ, Div Infect Dis, /Nashville//TN/37232; Vanderbilt Univ, Dept Microbiol & Immunol, /Nashville//TN/37232; Vanderbilt Univ, Dept Gastroenterol, /Nashville//TN/37232; Dept Vet Affairs Med Ctr, Med Serv, /Nashville//TN/37212
PUBLICATION TYPE: JOURNAL
PUBLICATION: GENE, 2000, V246, N1-2 (APR 4), P59-68
GENUINE ARTICLE#: 304NP
PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
ISSN: 0378-1119
LANGUAGE: English DOCUMENT TYPE: ARTICLE
ABSTRACT: The genetic organization and sequence heterogeneity of the iceA locus of Helicobacter *pylori"** was studied, and the existence of two distinct gene families, iceA1 and iceA2, at this locus was confirmed. iceA1 has significant sequence homology to nlaIIIR, encoding an endonuclease in Neisseria lactamica, but the similarity at the protein level is limited, due to frameshift mutations of iceA1 in most H. *pylori"** strains. In only five of the 19 iceA1 strains studied, a full-length open reading frame (ORF), capable of encoding a 228 aa protein, with 52% homology to NlaIII was observed. The region upstream of iceA2 is highly variable in length, containing up to 15 copies of 8 bp tandem repeats, iceA2 can encode proteins of 24, 59, 94, or 129 amino acids, consisting of 14 and 10 aa domains, conserved in all iceA2 strains, flanking 0, i, 2, or 3 copies of a 35 aa cassette. This 35 aa cassette consists of domains of 13, 16 and 6 aa, respectively. The 13 aa and 6 aa domains are highly conserved, but the 16 aa domain exists in two variants. In total, five distinct iceA2 subtypes were defined. Database searches did not reveal any homologous sequences. *Recombinant"** IceA1 and IceA2 proteins were expressed in Escherichia coli, confirming the predicted ORFs. Genotype-specific PCR primers permitted iceA genotyping in 318 (99.1%) of a worldwide collection of 321 H. *pylori"**, strains. The conserved sizes of the amplification products confirmed the worldwide distribution of discrete variants of iceA1 and iceA2.

9/3,AB/22 (Item 11 from file: 440)

11481777 References: 34
TITLE: Assessment of gastric carcinoma risk associated with Helicobacter pylori may vary depending on the antigen used - CagA specific enzyme-linked immunoadsorbent assay (ELISA) versus commercially available H-pylori ELISAs
AUTHOR(S): Maeda S (REPRINT); Yoshida H; Ogura K; Yamaji Y; Ikenoue T; Mitsushima T; Tagawa H; Kawaguchi R; Mori K; Mafune K; Kawabe T; Shiratori Y; Omata M
CORPORATE SOURCE: Univ Tokyo, Bunkyo Ku, 7-3-1 Hongo/Tokyo 1138655//Japan/ (REPRINT); Univ Tokyo, Bunkyo Ku, /Tokyo 1138655//Japan/; Kameda Gen Hosp, /Chiba//Japan/; Mitsui Mem Hosp, /Tokyo 101//Japan/; SRL Inc, Ctr Mol Biol & Cytogenet, /Tokyo//Japan/; Univ Tokyo, Dept Surg, /Tokyo 1138655//Japan/
PUBLICATION TYPE: JOURNAL
PUBLICATION: CANCER, 2000, V88, N7 (APR 1), P1530-1535
GENUINE ARTICLE#: 299RU
PUBLISHER: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012 USA
ISSN: 0008-543X
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: BACKGROUND. Previous epidemiologic studies produced inconsistent results when examining the relation between Helicobacter pylori infection and the risk of gastric carcinoma by measuring various anti-H. pylori antibodies. This study investigated the increased risk of cancer by examining different antibodies, including the specific anti-CagA antibody and antibodies from two commercially available kits.

METHODS. An ELISA for the detection of serum anti-CagA was established using a *recombinant"** CagA protein that the authors previously reported. Serum anti-CagA titer was determined for 80 patients with gastric carcinoma and 80 gender- and age-matched controls. Two anti-H. pylori antibodies from the commercially available kits HEL-p (Amrad, Kew Vie, Australia) and PLM-CAP (Enteric Product Inc., Westbury, NY) were also evaluated.

RESULTS. Anti-CagA seropositivity differed significantly between gastric carcinoma patients and controls (92.5% vs. 55.0%; P = 0.0001), showing an odds ratio of 10.4 (95% confidence interval [CI]: 4.23-29.74). The difference was less prominent for the seropositivity of HEL-p (77.5% vs. 58.8%; P = 0.0139; odds ratio: 2.38; 95% CI: 1.20-4.82) and insignificant for that of HM-CAP (65.0% vs. 57.5%; P = 0.4325; odds ratio: 1.30; 95% CI: 0.68-2.49).

CONCLUSIONS. The current study revealed that the antibody assay system used could be one important factor in the assessment of gastric carcinoma risk for patients with H. pylori. (C) 2000 American Cancer Society.

9/3,AB/23 (Item 12 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

11133428 References: 21
TITLE: A plasmid-based vector system for the cloning and expression of Helicobacter *pylori"** genes encoding outer membrane proteins
AUTHOR(S): Fischer W (REPRINT); Schwan D; Gerland E; Erlenfeld GE; Odenbreit S; Haas R
AUTHOR(S) E-MAIL: schmitt@m3401.mpk.med.umi-muenchen.de
CORPORATE SOURCE: Univ Munich, Max Von Pettenkofer Inst Hyg & Med Microbiol, Pettenkoferstr 9A/D-80336 Munich//Germany/ (REPRINT); Univ Munich, Max Von Pettenkofer Inst Hyg & Med Microbiol, /D-80336 Munich//Germany/
PUBLICATION TYPE: JOURNAL
PUBLICATION: MOLECULAR AND GENERAL GENETICS, 1999, V262, N3 (OCT), P501-507
GENUINE ARTICLE#: 258KU
PUBLISHER: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010 USA
ISSN: 0026-8925
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Helicobacter *pylori"** produces a number of proteins associated with the outer membrane, including adhesins and the *vacuolating"** *cytotoxin"**. We observed that the functional expression of such proteins is deleterious to Escherichia coli, the host bacterium used for gene cloning. Therefore, a general method was developed for the functional expression of such genes on a shuttle vector in H. *pylori"**, which has been termed SOMPES (Shuttle vector-based Outer Membrane Protein Expression System). The intact, active gene is reconstituted by recombination in H. *pylori"** from partial gene sequences cloned on an E. coli-H. *pylori"** shuttle vector. This system was established in an H. *pylori"** strain carrying a precise, unmarked chromosomal deletion of the *vacA"** gene,

which was constructed by adapting the streptomycin sensitivity system to H. *pylori"**. It is based on the expression of the H. *pylori"** rpsL gene as a counterselectable marker in the genetic background of an rpsL mutant. The utility of this approach is demonstrated by the expression of a *recombinant"** gene encoding *vacuolating"** *cytotoxin"** (*vacA"**) and a *recombinant"** gene encoding an adherence-associated outer membrane protein (alpA) in H. *pylori"**.

9/3,AB/24 (Item 13 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

10830761 References: 23
TITLE: Epidemiology of Helicobacter *pylori"** in chronic haemodialysis patients using the new RIBA (TM) H-*pylori"** SIA
AUTHOR(S): Fabrizi F (REPRINT); Martin P; Dixit V; Quan S; Brezina M; Abbey H; Gerosa S; Kaufman E; DiNello R; Polito A; Gitnick G
CORPORATE SOURCE: Lecco Hosp, Div Nephrol & Dialysis, Via Ghislanzoni 22/I-23900 Lecco//Italy/ (REPRINT); Lecco Hosp, Div Nephrol & Dialysis, /I-23900 Lecco//Italy/; Chiron Corp, /Emeryville//CA/94608; Univ Calif Los Angeles, Div Digest Dis, /Los Angeles//CA/
PUBLICATION TYPE: JOURNAL
PUBLICATION: NEPHROLOGY DIALYSIS TRANSPLANTATION, 1999, V14, N8 (AUG), P 1929-1933
GENUINE ARTICLE#: 224PD
PUBLISHER: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND
ISSN: 0931-0509
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Background. There are few data concerning the epidemiology of H. *pylori"** in patients on chronic haemodialysis (HD) treatment. These surveys concerned small populations and were made with ELISA technique. However, ELISA-based assays do not differentiate between strains of H. *pylori"** that are associated with ulcers. Recent literature reports that: formation of ulcers correlates strongly with the expression of *cytotoxin"**-associated protein (CagA) and *vacuolating"** *cytotoxin"** (*VacA"**) of H. *pylori"**.

Methods. A novel serological test (RIBA(TM) H. *pylori"** strip immunoblot assay (SIA)) has been recently introduced, it uses the H. *pylori"** lysate (Lys) along with two additional purified *recombinant"** antigens derived from CagA and VacA of H. *pylori"**. Aim. To study the epidemiology of H. *pylori"** using RIBA(TM) H. *pylori"** SIA among chronic HD patients and blood donors as a control group. In addition, the activity of H. *pylori"** was analysed by immunoblot technique in a group of patients with documented ulcers and normal renal function.

Results. The prevalence of antibody towards H. *pylori"** among HD patients, blood donors, and patients with documented ulcers was 56% (127/228), 53% (84/158), and 100% (21/21) respectively; the difference was significant (P = 0.0001). The frequency of anti-H. *pylori"**-positive individuals was significantly higher in patients with documented ulcers than HD patients and blood donors, 21/21 (100%) vs 211/386 (55%), P = 0.0001. The frequency of antibody to H. *pylori"** in the HD population was significantly associated with race (P = 0.005); no relationship between anti-H. *pylori"** antibody and numerous demographic, biochemical, and clinical features of patients was seen. The frequency of antibodies against

virulent strains of H. *pylori"** in HD patients and blood donors with H. *pylori"** was 60% (76/127) and 61% (51/84) respectively; it was 86% (18/21) among individuals with documented ulcers. No significant difference among these three groups occurred.

Conclusions. The frequency of antibody towards H. *pylori"** by RIBA(TM) H. *pylori"** SIA was high both in HD patients and blood donors; patients with documented ulcers and normal renal function had significantly higher frequency of anti-H. *pylori"** antibody. The anti-H. *pylori"** antibody rate among HD patients was strongly associated with race. The prevalence of antibody against virulent strains of H. *pylori"** did not change among HD patients and control groups. Studies in large cohorts of HD patients with documented peptic nicer disease are in progress.

9/3,AB/25 (Item 14 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

10412046 References: 81
TITLE: The attenuated Salmonella vaccine approach for the control of Helicobacter pylori-related diseases
AUTHOR(S): Gomez-Duarte OG; Bumann D; Meyer TF (REPRINT)
AUTHOR(S) E-MAIL: sinfbio@mpib-tuebingen.mpg.de
CORPORATE SOURCE: Max Planck Inst Biol, Abt Infektionsbiol, Spemannstr 34/D-72076 Tubingen//Germany/ (REPRINT); Max Planck Inst Biol, Abt Infektionsbiol, /D-72076 Tubingen//Germany/; Max Planck Inst Infektionsbiol, Mol Biol Abt, /D-10117 Berlin//Germany/
PUBLICATION TYPE: JOURNAL
PUBLICATION: VACCINE, 1999, V17, N13-14,SI (MAR 26), P1667-1673
GENUINE ARTICLE#: 178JM
PUBLISHER: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND
ISSN: 0264-410X
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: The Gram-negative bacterium Helicobacter pylori is a widespread human pathogen that colonizes the gastric mucosa and is associated with gastro-intestinal illnesses such as gastritis, peptic ulcer, gastric lymphoma and gastric cancer. Current pharmacological therapies are becoming less reliable for the control of H. pylori due to the elevated costs and to the increasing number of antibiotic resistant strains. New vaccination strategies utilizing H. pylori antigens combined with adjuvants or delivery of antigens by attenuated Salmonella strains have been successful in protecting mice against H. pylori infections. Oral immunization with single doses of urease-expressing Salmonella vaccine strains elicits mucosal and systemic antibody responses and fully protects different mouse strains against challenge infections with H. pylori. The high efficacy in the mouse model, combined with remarkable immunogenicity, safety and low-cost production, makes attenuated live *recombinant"** Salmonella promising vaccine candidates for the control of H, pylori-related diseases in humans.

9/3,AB/26 (Item 15 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

10254812 References: 48
TITLE: Therapeutic intragastric vaccination against Helicobacter pylori in mice eradicates an otherwise chronic infection and confers protection against reinfection
AUTHOR(S): Ghiara P (REPRINT); Rossi M; Marchetti M; Di Tommaso A; Vindigni C; Ciampolini F; Covacci A; Telford JL; De Magistris MT; Pizza M; Rappuoli R; Del Giudice G
AUTHOR(S) E-MAIL: Ghiara@iris02.biocine.it
CORPORATE SOURCE: Chiron Vaccines Immunobiol Res Inst, Dept Immunol, Via Fiorentina 1/I-53100 Siena//Italy/ (REPRINT); Chiron Vaccines Immunobiol Res Inst, Dept Immunol, /I-53100 Siena//Italy/; Univ Siena, Dept Environm Biol, /I-53100 Siena//Italy/; Univ Siena, Inst Pathol Anat & Histol, /I-53100 Siena//Italy/
PUBLICATION TYPE: JOURNAL
PUBLICATION: INFECTION AND IMMUNITY, 1997, V65, N12 (DEC), P4996-5002
GENUINE ARTICLE#: YJ227
PUBLISHER: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171 USA
ISSN: 0019-9567
LANGUAGE: English DOCUMENT TYPE: ARTICLE
ABSTRACT: Chronic infection of the gastroduodenal mucosae by the gram-negative spiral bacterium Helicobacter pylori is responsible for chronic active gastritis, peptic ulcers, and gastric cancers such as adenocarcinoma and low-grade gastric B-cell lymphoma. The success of eradication by antibiotic therapy is being rapidly hampered by the increasing occurrence of antibiotic-resistant strains. An attractive alternative approach to combat this infection is represented by the therapeutic use of vaccines. In the present work we have exploited the mouse model of persistent infection by mouse-adapted H. pylori strains that we have developed to assess the feasibility of the therapeutic use of vaccines against infection. We report that an otherwise chronic H. pylori infection in mice can be successfully eradicated by intragastric vaccination with H. pylori antigens such as *recombinant"** VacA and CagA, which were administered together with a genetically detoxified mutant of the heat-labile enterotoxin of Escherichia coli (referred to as LTK63), in which the serine in position 63 was replaced by a lysine. Moreover, we show that therapeutic vaccination confers efficacious protection against reinfection, These results represent strong evidence of the feasibility of therapeutic use of VacA- or CagA-based vaccine formulations against H. pylori infection in an animal model and give substantial preclinical support to the application of this kind of approach in human clinical trials.

9/3,AB/27 (Item 16 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

10163422 References: 61
TITLE: Emergence of *recombinant"** strains of Helicobacter pylori during human infection
AUTHOR(S): Kersulyte D; Chalkauskas H; Berg DE (REPRINT)
AUTHOR(S) E-MAIL: berg@borcim.wustl.edu
CORPORATE SOURCE: Washington Univ, Dept Mol Microbiol, Campus Box 8230,4566 Scott Ave/St Louis//MO/63110 (REPRINT); Washington Univ, Dept Mol Microbiol, /St Louis//MO/63110; Vilnius Univ Hosp, Gastroenterol Clin, /Vilnius//Lithuania/; Washington Univ, Dept Genet, /St Louis//MO/63110
PUBLICATION TYPE: JOURNAL

PUBLICATION: MOLECULAR MICROBIOLOGY, 1999, V31, N1 (JAN), P31-43
GENUINE ARTICLE#: 155NZ
PUBLISHER: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND
ISSN: 0950-382X
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Genetic recombination can be important evolutionarily in speeding the adaptation of organisms to new environments and in purging deleterious mutations. Here, we describe polymerase chain reaction (PCR), hybridization and DNA sequence-based evidence of six such exchanges between two strains of Helicobacter pylori during natural mixed infection of a patient in Lithuania. One parent strain contained the 37 kb long, virulence-associated cag pathogenicity island (PAI), and the other strain lacked this PAI. Most H. pylori from the patient had descended from the cag(+) parent, but had become cag(-) during infection. This had resulted from transfer of DNA containing the 'empty site' allele from the cag(-) strain and homologous recombination, not from excision of the cag PAI without DNA transfer. Other cases of recombination involved genes for an outer membrane protein (omp5 and omp29; also called HP0227 and HP1342) and a putative phosphoenolpyruvate synthase (ppsA; HP0121). Replacement of a short patch of DNA sequence (36-124 bp) was also seen. As the chance of forming any given *recombinant"** is small, the abundance of *recombinants"** in this patient suggests selection for particular *recombinant"** genotypes during years of chronic infection. We suggest that genetic exchange among unrelated H. pylori strains, as documented here, is important because of the diversity of this gastric pathogen and its human hosts. Certain H. pylori *recombinants"** may grow better in a given host than either parent. The vigour of growth, in turn, could impact on the severity of disease that infection can elicit.

9/3,AB/28 (Item 17 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

10112727 References: 42
TITLE: Relationship of *vacA"** genotypes of Helicobacter *pylori"** to cagA status, *cytotoxin"** production, and clinical outcome
AUTHOR(S): Yamaoka Y (REPRINT); Kodama T; Kita M; Imanishi J; Kashima K; Graham DY
AUTHOR(S) E-MAIL: yyamaoka@bcm.tmc.edu
CORPORATE SOURCE: Vet Affairs Med Ctr 111D, Dept Med, 2002 Holcombe Blvd/Houston//TX/77030 (REPRINT); Vet Affairs Med Ctr 111D, Dept Med, /Houston//TX/77030; Baylor Coll Med, /Houston//TX/77030; Kyoto Prefectural Univ Med, Dept Internal Med 3, /Kyoto 602//Japan/; Kyoto Prefectural Univ Med, Dept Microbiol, /Kyoto 602//Japan/
PUBLICATION TYPE: JOURNAL
PUBLICATION: HELICOBACTER, 1998, V3, N4 (DEC), P241-253
GENUINE ARTICLE#: 149HX
PUBLISHER: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148 USA
ISSN: 1083-4389
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Background. Mosaicism in *vacA"** alleles with three distinct families of *vacA"** signal sequences (s1a, s1b and s2) and two distinct families of middle region alleles (m1 and m2) has been reported. It was suggested that the *vacA"** s1a genotype was closely associated with

duodenal ulcer disease and with high *cytotoxin"** production. The aim of this study was to evaluate the role of *vacA"** genotyping with respect to gastric inflammation and injury, *cytotoxin"** activity, and clinical presentation.

Methods. H. *pylori"** from patients with gastritis, peptic ulcer disease, or gastric cancer were characterized by *vacA"** typing by polymerase chain reaction (PCR) and DNA sequencing. In vitro *cytotoxin"** activity was assessed by *vacuolation"** assay using Vero cells as well as with Hela cells.

Results. Four hundred ninety-one strains were tested. *vacA"** genotype s1a/m1 was present in more than 95% of strains independent of presentation with gastritis, peptic ulcer, or gastric cancer. No *vacA"** genotype was associated with high average *cytotoxin"** activity. The s2/m2 isolates had low or absent *cytotoxin"** activity. All cagA negative strains (n = 18) were s1a strains and both s2/m2 strains were cagA positive. One strain that was a *recombinant"** of mi and m2 strains was identified and had low *cytotoxin"** activity. The nucleotide and amino acid sequences between original mi strains and Japanese mi strains (new mi strains) were about 85% and 81%, respectively. Strains with the new mi genotype had nucleotide and amino acid sequences similarity of more than 96%. There was no difference in *cytotoxin"** activity between strains with the Western type mi and the new type mi genotype.

Conclusion. In this as in other reported studies (approximate to 1500 patients overall) *vacA"** genotype was strongly but not exclusively associated with the presence of cagA. Overall, the studies did not support a role for *vacA"** genotyping in relation to *cytotoxin"** activity, virulence, histologic finding, or risk of a particular H. *pylori"** disease. *vacA"** genotype s1 is likely to be a surrogate marker for the presence of the cag pathogenicity.

9/3,AB/29 (Item 18 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

09651647 References: 26
TITLE: Variants of the 3' region of the cagA gene in Helicobacter pylori isolates from patients with different H-pylori associated diseases
AUTHOR(S): Yamaoka Y; Kodama T; Kashima K; Graham DY; Sepulveda AR (REPRINT)
CORPORATE SOURCE: VET AFFAIRS MED CTR,DEPT MED, 111D, 2002 HOLCOMBE BLVD/HOUSTON//TX/77030 (REPRINT); VET AFFAIRS MED CTR,DEPT MED/HOUSTON//TX/77030; BAYLOR COLL MED,/HOUSTON//TX/77030; KYOTO PREFECTURAL UNIV MED,DEPT INTERNAL MED 3, KAMIKYO KU/KYOTO 602//JAPAN/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF CLINICAL MICROBIOLOGY, 1998, V36, N8 (AUG), P 2258-2263
GENUINE ARTICLE#: ZZ359
PUBLISHER: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171
ISSN: 0095-1137
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: The CagA protein of Helicobacter pylori is an immunogenic antigen of variable size and unknown function that has been associated with

increased virulence as well as two mutually exclusive diseases, duodenal ulcer and gastric carcinoma. The 3' region of the cagA gene contains repeated sequences. To determine whether there are structural changes in the 3' region of cagA that predict outcome of H. pylori infection, we examined 155 cagA gene-positive H. pylori isolates from Japanese patients including 50 patients with simple gastritis, 40 with gastric ulcer, 35 with duodenal ulcer, and 30 with gastric cancer. The 3' region of the cagA gene was amplified by PCR followed by sequencing. CagA proteins were detected by immunoblotting using a polyclonal antibody against *recombinant"** CagA. One hundred forty-five strains yielded PCR products of 642 to 651 bp; 10 strains had products of 756 to 813 bp. The sequence of the 3' region of the cagA gene in Japan differs markedly from the primary sequence of cagA genes from Western isolates. Sequence analysis of the PCR products showed four types of primary gene structure (designated types A, B, C, and D) depending on the type and number of repeats. Six of the seven type C strains were found in patients with gastric cancer ($P < 0.01$ in comparison to noncancer patients). Comparison of type A and type C strains from patients with gastric cancer showed that type C was associated with higher levels of CagA antibody and more severe degrees of atrophy. Differences in cagA genotype may be useful for molecular epidemiology and may provide a marker for differences in virulence among cagA-positive H. pylori strains.

9/3,AB/30 (Item 19 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

08210076 References: 0
TITLE: Vaccinating against Helicobacter *pylori"** infections: Reality and perspectives
AUTHOR(S): Labigne A (REPRINT); Ferrero R; Galmiche JP
CORPORATE SOURCE: INST PASTEUR,INSERM, U389, UNITE PATHOGENIE BACTERIENNE MUQUEUSES, 25 RUE DOCTEUR ROUX/F-75724 PARIS 15//FRANCE/ (REPRINT)
PUBLICATION TYPE: BOOK
PUBLICATION: UPDATE GASTROENTEROLOGY 1996, 1996, P49-54
GENUINE ARTICLE#: BH18H
PUBLISHER: JOHN LIBBEY EUROTEXT, 127 AVE DE LA REPUBLIQUE, 92120 MONTROUGE, FRANCE
ISBN: 2-7420-0150-6
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: The high prevalence of Helicobacter *pylori"** infections, the severity of certain associated pathologies (duodenal ulcers, lymphoma, gastric carcinoma) and the predictable gradual emergence of resistance to the antibiotics currently used are factors that have encouraged the development of a vaccine approach to H. *pylori"** infections. Studies to date have demonstrated that it is possible to protect animals (mice, ferrets, cats) against Helicobacter infection by immunisation via the oral-gastric route using crude extracts of bacterial antigens combined with an adjuvant known to stimulate a mucosal immune response. More recently, better defined H. *pylori"** antigens such as the urease subunits, the HspA protein or the *VacA"** *cytotoxin"**, have been identified as possible components of a *recombinant"** subunit vaccine. Progress achieved over the last few years in animal models leads us to expect that a prophylactic and/or therapeutic vaccine will be a reality in the first decade of the 21st century.

9/3,AB/31 (Item 20 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

07835725 References: 31
TITLE: Relationship of immune response to heat-shock protein A and characteristics of Helicobacter pylori-infected patients
AUTHOR(S): PerezPerez GI; Thiberge JM; Labigne A; Blaser MJ
CORPORATE SOURCE: VANDERBILT UNIV,SCH MED, DIV INFECT DIS, A-3310 MED CTR N, 1161 21ST AVE S/NASHVILLE//TN/37232 (REPRINT); DEPT VET AFFAIRS MED CTR,INFECT DIS SECT/NASHVILLE//TN/37212; INST PASTEUR,UNITE PATHOGENIE BACTERIENNE MUQUEUSES, INSERM U389/PARIS//FRANCE/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF INFECTIOUS DISEASES, 1996, V174, N5 (NOV), P 1046-1050
GENUINE ARTICLE#: VN181
PUBLISHER: UNIV CHICAGO PRESS, 5720 S WOODLAWN AVE, CHICAGO, IL 60637
ISSN: 0022-1899
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Heat-shock protein A (HspA) is a GroES homolog in Helicobacter pylori. Using a *recombinant"** HspA-maltose-binding protein fusion, the serologic responses to HspA were determined. For 139 H. pylori-uninfected persons, responsesto HspA were low-level or absent. In a survey of 273 infected persons, 105(38.5%) were seropositive; there was no relationship between clinical outcome of infection and HspA seropositivity. Using paired sera obtained from 39 subjects (mean, 7.1 years apart), the stability of seroresponsiveness to HspA was examined, Far 34 persons there was no change in status between thepaired sera, but 5 (20%) of 25 initially seronegative persons seroconverted. The hypothesis that HspA seropositivity was related to patient age was examined using sera from 121 asymptomatic H. pylori-infected persons. Both the HspA seropositivity rate and the intensity of the response rose with age. In total, these findings indicate that HspA seropositivity is not universal but may be a consequence of prolonged H. pylori infection.

9/3,AB/32 (Item 21 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

06424781 References: 40
TITLE: SEROLOGIC DETECTION OF INFECTION WITH CAGA(+) HELICOBACTER PYLORI STRAINS
AUTHOR(S): COVER TL; GLUPCZYNSKI Y; LAGE AP; BURETTE A; TUMMURU MKR; PEREZPEREZ GI; BLASER MJ
CORPORATE SOURCE: VANDERBILT UNIV,SCH MED,DEPT MED,DIV INFECT DIS,MED CTR N A3310/NASHVILLE//TN/37232 (Reprint); VANDERBILT UNIV,SCH MED,DEPT MICROBIOL/NASHVILLE//TN/37212; VET AFFAIRS MED CTR/NASHVILLE//TN/37212; HOP ANDRE VESALE,BACTERIOL LAB/MONTIGNIES TILLEUL//BELGIUM/; NOUVELLE CLIN BASILIQUE,DEPT GASTROENTEROL/BRUSSELS//BELGIUM/
PUBLICATION: JOURNAL OF CLINICAL MICROBIOLOGY, 1995, V33, N6 (JUN), P 1496-1500
GENUINE ARTICLE#: QZ723
ISSN: 0095-1137
LANGUAGE: ENGLISH DOCUMENT TYPE: ARTICLE

ABSTRACT: Approximately 60% of Helicobacter pylori isolates possess the

cagA gene and express its 120- to 140-kDa product (CagA). In this study, the cagA gene was detected in H. pylori isolates from 26 (81.3%) of 32 patients with duodenal ulcers (DU), 17 (68.0%) of 25 patients with gastric ulcers, and 23 (59.0%) of 39 patients with nonulcer dyspepsia (NUD), By Western blotting (immunoblotting) with antiserum to CagA, in vitro CagA expression was demonstrated for 95.5% of cagA(+) strains compared with 0% of strains lacking cagA. Sera from patients infected with cagA(+) strains (n = 66) reacted with *recombinant"** CagA in an enzyme-linked immunosorbent assay to a significantly greater extent than either sera from patients infected with strains lacking cagA (n = 30) or sera from uninfected persons (n = 25) ($P < 0.001$), A strain lacking cagA was isolated from eight patients who had serum immunoglobulin G antibodies to CagA, which suggests that these patients were infected with multiple strains, Serum immunoglobulin G antibodies to CagA were present in 87.5, 76.0, and 56.4% of patients with DU, gastric ulcers, and NUD, respectively (odds ratio, 5.41; 95% confidence interval, 1.44 to 24.72; $P = 0.004$ [DU versus NUD]), These data demonstrate an association between infection with cagA(+) H, pylori and the presence of duodenal ulceration and indicate that serologic testing is a sensitive method for detecting infection with cagA(+) strains.

9/3,AB/33 (Item 22 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

04980851 References: 0
(NO REFS KEYED)
TITLE: MOLECULAR ANALYSIS OF THE HELICOBACTER-PYLORI CYTOTOXIN GENE
AUTHOR(S): TELFORD JL; DELLORCO M; BURRONI D; COMANDUCCI M; BUGNOLI M; FIGURA N; COVACCI A; RAPPUOLI R
CORPORATE SOURCE: IMMUNOBIOL RES INST SIENA,VIA FIORENTINA 1/I-53100 SIENA//ITALY/ (Reprint)
PUBLICATION: EUROPEAN JOURNAL OF GASTROENTEROLOGY & HEPATOLOGY, 1993, V5, S2 (OCT), PS22-S24
GENUINE ARTICLE#: ME638
ISSN: 0954-691X
LANGUAGE: ENGLISH DOCUMENT TYPE: ARTICLE

ABSTRACT: Objective: To assess the contribution of the *vacuolating"** *cytotoxin"** to Helicobacter pylori virulence.

Design: Approximately 50% of clinical isolates of H. pylori produce a potent *vacuolating"** *cytotoxin"** and a *cytotoxin"**-associated protein with a molecular weight of 128000 (CagA). A molecular genetic analysis of cytotoxin-positive and -negative strains was performed to clarify the effects of this cytotoxin in H. pylori virulence.

Methods: We used the polymerase chain reaction and molecular cloning to obtain the gene coding for the cytotoxin. Cytotoxin-positive and -negative strains of H. pylori were analysed by DNA hybridization and the use of antisera raised against the *recombinant"** cytotoxin.

Results: We cloned the entire gene coding for the cytotoxin and raised antisera against the gene product. This gene proved to be unrelated to the gene coding for the cytotoxin-associated protein (cagA gene). The protein was not produced by cytotoxin-negative strains of H. pylori, although cagA gene sequences were present in the genome.

Conclusions: Although the cagA gene was absent in cytotoxin-negative H. pylori strains, the cytotoxin gene was present, but not expressed, suggesting that the cagA gene may regulate cytotoxicity.

9/3,AB/34 (Item 23 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

04634191 References: 43
TITLE: MOLECULAR CHARACTERIZATION OF THE 128-KDA IMMUNODOMINANT ANTIGEN OF HELICOBACTER-PYLORI ASSOCIATED WITH CYTOTOXICITY AND DUODENAL ULCER
AUTHOR(S): COVACCI A; CENSINI S; BUGNOLI M; PETRACCA R; BURRONI D; MACCHIA G; MASSONE A; PAPINI E; XIANG ZY; FIGURA N; RAPPUOLI R (Reprint)
CORPORATE SOURCE: IMMUNOBIOL RES INST SIENNA,VIA FIORENTINA 1/I-53100 SIENA//ITALY/ (Reprint); IMMUNOBIOL RES INST SIENNA,VIA FIORENTINA 1/I-53100 SIENA//ITALY/; UNIV PADUA,DIPARTIMENTO SCI BIOMED/I-35121 PADUA//ITALY/; UNIV SIENA,IST PATOL MED/I-53100 SIENA//ITALY/
PUBLICATION: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, 1993, V90, N12 (JUN 15), P5791-5795
GENUINE ARTICLE#: LH129
ISSN: 0027-8424
LANGUAGE: ENGLISH DOCUMENT TYPE: ARTICLE

ABSTRACT: Helicobacter pylori has been associated with gastritis, peptic ulcer, and gastric adenocarcinoma. We report the nucleotide sequence and expression of an immunodominant antigen of H. pylori and the immune response to the antigen during disease. The antigen, named CagA (cytotoxin-associated gene A), is a hydrophilic, surface-exposed protein of 128 kDa produced by most clinical isolates. The size of the cagA gene and its protein varies in different strains by a mechanism that involves duplication of regions within the gene. Clinical isolates that do not produce the antigen do not have the gene and are unable to produce an active *vacuolating"** *cytotoxin"**. An ELISA to detect the immune response against a *recombinant"** fragment of this protein detects 75.3% of patients with gastroduodenal diseases and 100% of patients with duodenal ulcer ($P < 0.0005$), suggesting that only bacteria harboring this protein are associated with disease.

9/3,AB/35 (Item 24 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

04516425 References: 43
TITLE: CLONING AND EXPRESSION OF A HIGH-MOLECULAR-MASS MAJOR ANTIGEN OF HELICOBACTER-PYLORI - EVIDENCE OF LINKAGE TO CYTOTOXIN PRODUCTION
AUTHOR(S): TUMMURU MKR; COVER TL; BLASER MJ (Reprint)
CORPORATE SOURCE: VANDERBILT UNIV,MED CTR,SCH MED,DEPT MED,DIV INFECT DIS/NASHVILLE//TN/37232 (Reprint); VANDERBILT UNIV,MED CTR,SCH MED,DEPT MED,DIV INFECT DIS/NASHVILLE//TN/37232; DEPT VET AFFAIRS MED CTR/NASHVILLE//TN/37212
PUBLICATION: INFECTION AND IMMUNITY, 1993, V61, N5 (MAY), P1799-1809
GENUINE ARTICLE#: KZ177
ISSN: 0019-9567
LANGUAGE: ENGLISH DOCUMENT TYPE: ARTICLE

ABSTRACT: A high-molecular-mass (120- to 128-kDa) Helicobacter pylori

antigen has been associated with peptic ulcer disease. We created a bank of 40,000 random chromosomal fragments of H. pylori 84-183 by using lambdaZapII. Screening of this bank in Escherichia coli XL1-Blue with absorbed serum from an H. pylori-infected person permitted the isolation and purification of a clone with a 3.5-kb insert. Subcloning of this insert (pMC3) permitted the expression of a *recombinant"** H. pylori protein that had a mass of approximately 96 kDa and that was recognized by the human serum. Sera that were obtained from H. pylori-infected persons and that recognized the native 120- to 128-kDa H. pylori antigen recognized the *recombinant"** 96-kDa pMC3 protein to a significantly greater extent than did sera that did not recognize the native H. pylori antigen. All 19 H. pylori isolates producing the 120- to 128-kDa antigen hybridized with pMC3; none of 13 nonproducers did so ($P < 0.001$). Because all 15 isolates producing the *vacuolating"** *cytotoxin"** hybridized with pMC3, we called the gene cagA (cytotoxin-associated gene). Sequence analysis of pMC3 identified an open reading frame of 859 amino acids, without a termination codon. Parallel screening of a lambdagt11 library with human serum revealed positive plaques with identical 0.6-kb inserts and sequences matching the sequence of the downstream region of pMC3. To clone the full-length gene, we used the 0.6-kb fragment as a probe and isolated a clone with a 2.7-kb insert from the lambdaZaplI genomic library. Nucleotide sequencing of this insert (pYB2) revealed a 785-bp sequence that overlapped the downstream region of pMC3. Translation of the complete nucleotide sequence of cagA revealed an open reading frame of 1,181 amino acids yielding a protein of 131,517 daltons. There was no significant homology with any previously reported protein sequence. These findings indicate the cloning and characterization of a high-molecular-mass H. pylori antigen potentially associated with virulence and with cytotoxin production.

9/3,AB/36 (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01103641
Helicobacter pylori cytotoxin useful for vaccines and diagnostics
Helicobacter pylori Cytotoxin verwendbar in Impfstoffe und Diagnostik
Cytotoxine d' Helicobacter pylori utile dans des vaccins et en diagnostique
PATENT ASSIGNEE:
Chiron S.P.A., (2376150), Via Fiorentina, 1, 53100 Siena, (IT),
(Applicant designated States: all)
INVENTOR:
Covacci, Antonello, Via Fiorentina 1, 53100 Siena, (IT)
Bugnoli, Massimo, Via Fiorentina 1, 53100 Siena, (IT)
Telford, John, Via Fiorentina 1, 53100 Siena, (IT)
Macchia, Giovanni, Via Fiorentina 1, 53100 Siena, (IT)
Rappuoli, Rino, Via Fiorentina 1, 53100 Siena, (IT)
LEGAL REPRESENTATIVE:
Hallybone, Huw George (53031), CARPMAELS AND RANSFORD 43 Bloomsbury Square, London WC1A 2RA, (GB)
PATENT (CC, No, Kind, Date): EP 967279 A1 991229 (Basic)
APPLICATION (CC, No, Date): EP 99202698 930302;
PRIORITY (CC, No, Date): IT 92FI52 920302; WO EPPCT 930125
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
RELATED PARENT NUMBER(S) - PN (AN):
EP 643770 (EP 93905285)
INTERNATIONAL PATENT CLASS: C12N-015/31; A61K-039/106; C12Q-001/68;

G01N-033/569

ABSTRACT EP 967279 A1

Helicobacter pylori is known to cause or be a cofactor in type B gastritis, peptic ulcers, and gastric tumors. In both developed and developing countries, a high percentage of people are infected with this bacterium. The present invention relates generally to certain H. pylori proteins, to the genes which express these proteins, and to the use of these proteins for diagnostic and vaccine applications. Specifically, molecular cloning, nucleotide, and amino acid sequences for the H. pylori cytotoxin (CT), the "Cytotoxin Associated Immunodominant" (CAI) antigen, and the heat shock protein (hsp60) are described herein.

ABSTRACT WORD COUNT: 94

NOTE:
Figure number on first page: NONE

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	199952	578
SPEC A	(English)	199952	18870
Total word count - document A			19448
Total word count - document B			0
Total word count - documents A + B			19448

9/3,AB/37 (Item 2 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00979494
Attenuated Vibrio cholerae strains
Abgeschwachte Stamme von Vibrio cholerae
Souches attenuees de Vibrio cholerae
PATENT ASSIGNEE:
Chiron S.P.A., (2376150), Via Fiorentina, 1, 53100 Siena, (IT),
(Applicant designated States: all)
INVENTOR:
Fontana, Mariarita, Via del Colle, 19, 53100 Siena, (IT)
Pizza, Mariagrazina, Strada di Montalbuccio, 160, 53100 Siena, (IT)
Rappuoli, Rino, Via Calamandrei, 39, Quercegrossa, 53010 Monteriggioni (SI), (IT)
LEGAL REPRESENTATIVE:
Hallybone, Huw George (53031), CARPMAELS AND RANSFORD 43 Bloomsbury Square, London WC1A 2RA, (GB)
PATENT (CC, No, Kind, Date): EP 887403 A2 981230 (Basic)
EP 887403 A3 001206
APPLICATION (CC, No, Date): EP 98305060 980626;
PRIORITY (CC, No, Date): GB 9713664 970627; GB 9722435 971023
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: C12N-001/20; C12N-001/21; C12R-001/63; C12N-001/36; C12N-015/74; A61K-039/106; A61K-039/10; C07K-014/245

ABSTRACT EP 887403 A2

The present invention relates to attenuated strains of Vibrio cholerae and their use as carrier agents for antigens in the mammalian body. The

attenuated strains of the present invention can be used as carriers for both heterologous and homologous antigens. The strains of the present invention colonise the human intestine efficiently yet safely and generate antibodies with high bacteriocidal or anti-viral activity.
ABSTRACT WORD COUNT: 63
NOTE:
Figure number on first page: NONE

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	9853	460
SPEC A	(English)	9853	7166
Total word count - document A			7626
Total word count - document B			0
Total word count - documents A + B			7626

9/3,AB/38 (Item 3 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00969625
HELICOBACTER *PYLORI"** DIAGNOSTICS
HELICOBACTER *PYLORI"** DIAGNOSTIKA
DIAGNOSTICS DE L'HELICOBACTER *PYLORI"**
PATENT ASSIGNEE:
CHIRON CORPORATION, (572530), 4560 Horton Street, Emeryville, California 94608, (US), (Proprietor designated states: all)
INVENTOR:
QUAN, Stella, Chiron Corporation, 4560 Horton Street, Emeryville, CA 94608, (US)
VALENZUELA, Pablo, 2919 Avalon Avenue, Berkeley, CA 94705, (US)
POLITO, Alan, Chiron Corporation, 4560 Horton Street, Emeryville, CA 94608, (US)
LEGAL REPRESENTATIVE:
Hallybone, Huw George et al (53031), Carpmaels and Ransford, 43 Bloomsbury Square, London WC1A 2RA, (GB)
PATENT (CC, No, Kind, Date): EP 946874 A1 991006 (Basic)
EP 946874 B1 020605
WO 9827432 980625
APPLICATION (CC, No, Date): EP 97953172 971218; WO 97US22798 971218
PRIORITY (CC, No, Date): US 33707 P 961219
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: G01N-033/569; G01N-033/543
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	200223	1184
CLAIMS B	(German)	200223	1048
CLAIMS B	(French)	200223	1536
SPEC B	(English)	200223	10200
Total word count - document A			0
Total word count - document B			13968
Total word count - documents A + B			13968

9/3,AB/39 (Item 4 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00915757
Helicobacter *pylori"** live vaccine
Helicobacter *Pylori"** Lebendimpfstoff
Vaccin vivant d'helicobacter *pylori"**
PATENT ASSIGNEE:
Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V. Berlin, (210793), Hofgartenstrasse 2, 80539 Munchen, (DE),
INVENTOR:
Meyer, Thomas, Prof.Dr., Spemannstrasse 30, 72076 Tubingen, (DE)
GOmez, Oscar, Dr., Eduard-Spranger-Strasse 34, 72076 Tubingen, (DE)
Yan, Zhengxin, Dr., Fichtenweg 6, 72076 Tubingen, (DE)
Haas, Rainer, Dr., Usrainer Ring 65, 72076 Tubingen, (DE)
Lucas, Bernadette, Dr., Eduard-Spranger-Strasse 26, 72076 Tubingen, (DE)
LEGAL REPRESENTATIVE:
Weiss, Wolfgang, Dipl.-Chem. Dr. et al (75611), Patentanwalte Weickmann & Partner, Kopernikusstrasse 9, 81679 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 835928 A1 980415 (Basic)
APPLICATION (CC, No, Date): EP 96116337 961011;
PRIORITY (CC, No, Date): EP 96116337 961011
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: C12N-001/21

ABSTRACT EP 835928 A1
The present invention relates to novel *recombinant"** live vaccines, which provide protective immunity against an infection by Helicobacter *pylori"** and a method of screening H. *pylori"** antigens for optimized vaccines.
ABSTRACT WORD COUNT: 31

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	9816	525
SPEC A	(English)	9816	3736
Total word count - document A			4261
Total word count - document B			0
Total word count - documents A + B			4261

9/3,AB/40 (Item 5 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00665271
DNA POLYMERASES WITH ENHANCED THERMOSTABILITY AND ENHANCED LENGTH AND EFFICIENCY OF PRIMER EXTENSION
DNS-POLYMERASEN MIT ERHOHTER TEMPERATURSTABILITAT UND VERGROSSTERTER LANGE UND EFFIZIENT DER PRIMER-VERLANGERUNG
ADN POLYMERASES PRESENTANT UNE EXTENSION D'AMORCE DE THERMOSTABILITE, DE LONGUEUR ET D'EFFICACITE ACCRUES
PATENT ASSIGNEE:

Takara Shuzo Co, Ltd., (710325), Otsu, Shiga, (JP), (applicant designated states: AT;BE;CH;DE;DK;ES;FR;GB;GR;IE;IT;LI;LU;MC;NL;PT;SE)
INVENTOR:
Barnes, Wayne M., 223 Renaldo Drive, Chesterfield, Missouri 63017, (US)
LEGAL REPRESENTATIVE:
Allard, Susan Joyce et al (27611), BOULT WADE TENNANT, 27 Furnival Street , London EC4A 1PQ, (GB)
PATENT (CC, No, Kind, Date): EP 693078 A1 960124 (Basic)
EP 693078 A1 970625
EP 693078 B1 990623
WO 9426766 941124
APPLICATION (CC, No, Date): EP 94909742 940222; WO 94US1867 940222
PRIORITY (CC, No, Date): US 21623 930219
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: C12N-015/54; C12N-009/12; C12Q-001/68;
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	9925	1774
CLAIMS B	(German)	9925	1623
CLAIMS B	(French)	9925	1843
SPEC B	(English)	9925	18097
Total word count - document A			0
Total word count - document B			23337
Total word count - documents A + B			23337

9/3,AB/41 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0232642 DBA Accession No.: 99-02743 PATENT
New attenuated Vibrio cholerae strains expressing heterologous antigen - attenuated *recombinant"** bacterium preparation; heterologous protein e.g. Escherichia coli or Bacillus pertussis antigen expression for use as *recombinant"** vaccine
AUTHOR: Fontana M; Pizza M; Rappuoli R
CORPORATE SOURCE: Siena, Italy.
PATENT ASSIGNEE: Chiron 1998
PATENT NUMBER: EP 887403 PATENT DATE: 981230 WPI ACCESSION NO.: 99-047871 (9905)
PRIORITY APPLIC. NO.: GB 9722435 APPLIC. DATE: 971023
NATIONAL APPLIC. NO.: EP 98305060 APPLIC. DATE: 980626
LANGUAGE: English
ABSTRACT: A new attenuated Vibrio cholerae strain expresses a heterologous antigen that is not derived from an enteropathic bacterium. Also new are an immunogenic composition for use as a vaccine consisting of the new bacterium in conjunction with a pharmaceutically-acceptable carrier, and a method for therapy or prevention of a disease in a subject which involves administering the vaccine. V. cholerae is ideal for use as a vaccine as it is non-invasive and has the ability to maintain a balance between its ability to colonize the human intestine and invoke an immune response, and its reactogenicity. The attenuated strain is IEM101 and the heterologous antigen is preferably an antigen from Bacillus pertussis or Helicobacter pylori. The toxin may be:

cytotoxicity-associated immunodominant antigen; *vacuolating"** *cytotoxin"** -A; the heat labile enterotoxin of Escherichia coli, optionally mutated at position-63 of the wild-type sequence. When the antigen is a neutrophil activating protein, the toxin is fragment-C of the tetanus toxin or the tracheal colonization factor of B. pertussis. (16pp)

9/3,AB/42 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0197939 DBA Accession No.: 96-08710 PATENT
Fermentation of Helicobacter pylori in production of *vacuolating"** *cytotoxin"** - fed-batch culture with glucose addition and purification for use as a vaccine
AUTHOR: Olivieri R; Rappuoli R; Telford J L
CORPORATE SOURCE: Siena, Italy.
PATENT ASSIGNEE: Biocine 1996
PATENT NUMBER: WO 9614393 PATENT DATE: 960517 WPI ACCESSION NO.: 96-251746 (9625)
PRIORITY APPLIC. NO.: GB 9422331 APPLIC. DATE: 941104
NATIONAL APPLIC. NO.: WO 95IB1007 APPLIC. DATE: 951106
LANGUAGE: English
ABSTRACT: A new method for culturing Helicobacter pylori to produce a *vacuolating"** *cytotoxin"** involves use of a culture medium containing more than 1 g/l glucose, e.g. in Brucella broth supplemented with glucose and blood products or cyclodextrin. The glucose may be supplied by multiple shot or continuous feeding in a fed-batch culture process, and may be maintained at 2-6 g/l throughout the culture period. The cytotoxin may be purified by adsorption on a cellulose sulfate adsorbent and elution in a salt gradient. Culture supernatant is concentrated (by ammonium sulfate precipitation, or tangential flow filtration and diafiltration) and proteins are suspended in buffer containing 100 mM NaCl, followed by adsorption on the column, elution in 0.1-1.5 M NaCl in phosphate buffer, pH 6.5, and optionally concentrating the cytotoxin further and subjecting to gel filtration on a controlled pore matrix. The product may be used as a vaccine. Addition of glucose increases the growth rate, and increases cytotoxin productivity from 5 mg/l to 19 mg/l. Adsorption on cellulose sulfate gives yields of 15-20%, compared to 0.5% on phenyl-Sepharose. (29pp)

Set	Items	Description
S10	172	AU=(COVACCI, A? OR COVACCI A?)
S11	112	AU=(BUGNOLI, M? OR BUGNOLI M?)
S12	486	AU=(TELFORD, J? OR TELFORD J?)
S13	876	AU=(RAPPUOLI, R? OR RAPPUOLI R?)
S14	126	AU=(MACCHIA, G? OR MACCHIA G?)
S15	2	S10 AND S11 AND S12 AND S13 AND S14
S16	102	S10 AND (S11 OR S12 OR S13 OR S14)
S17	67	S11 AND (S12 OR S13 OR S14)
S18	125	S12 AND (S13 OR S14)
S19	8	S13 AND S14
S20	94	(S16 OR S17 OR S18 OR S10 OR S11 OR S12 OR S13 OR S14) AND (S1 OR S5)
S21	15	S20 AND RECOMBINAN?
S22	6	(S15 OR S19 OR S21) NOT S8
S23	3	RD (unique items)

Author(s)

Searcher : Shears 308-4994

>>>No matching display code(s) found in file(s): 65, 113

23/3,AB/1 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

11189950 PASCAL No.: 94-0006743
The Hsp60 protein of Helicobacter pylori : structure and immune response in patients with gastroduodenal diseases
*MACCHIA G"**; MASSONE A; BURRONI D; COVACCI A; CENSINI S; *RAPPUOLI R"**
IRIS immunobiological res. inst., 53100 Siena, Italy
Journal: Molecular microbiology, 1993, 9 (3) 645-652
Language: English
Helicobacter pylori is a human pathogen that has been associated with gastritis, peptic ulcer and gastric carcinoma. The role of the direct action of H. pylori virulence factors and of the induction of autoreactive immunity in the development of chronic gastritis has not been clarified yet. Here we report the cloning and molecular characterization of a gene of H. pylori coding for a protein of 58kDa, recognized by sera of patients affected by H. pylori-induced gastroduodenal diseases. This antigen is present in all the H. pylori strains tested and it belongs to the Hsp60 family of heat-shock proteins, with high homology with other bacterial and eukaryotic proteins of the same family

23/3,AB/2 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal

11089952 PASCAL No.: 93-0596973
Molecular characterization of the 128-kDa immunodominant antigen of Helicobacter pylori associated with cytotoxicity and duodenal ulcer
COVACCI A; CENSINI S; BUGNOLI M; PETRACCA R; BURRONI D; *MACCHIA G"**; MASSONE A; PAPINI E; ZHAOYING XIANG; FIGURA N; *RAPPUOLI R"**
Immunobiological res. inst. Siena, 53100 Siena, Italy
Journal: Proceedings of the National Academy of Sciences of the United States of America, 1993, 90 (12) 5791-5795
Language: English
Helicobacter pylori has been associated with gastritis, peptic ulcer, and gastric adenocarcinoma. We report the nucleotide sequence and expression of an immunodominant antigen of H. pylori and the immune response to the antigen during disease. The antigen, named CagA (cytotoxin-associated gene A), is a hydrophilic, surface-exposed protein of 128 kDa produced by most clinical isolates. The size of the cagA gene and its protein varies in different strains by a mechanism that involves duplication of regions within the gene. Clinical isolates that do not produce the antigen do not have the gene and are unable to produce an active vacuolating cytotoxin

23/3,AB/3 (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00671135
HELICOBACTER PYLORI PROTEINS USEFUL FOR VACCINES AND DIAGNOSTICS.
Helicobacter Pylori Proteine verwendbar in Impfstoffen und Diagnose.
PROTEINES D'HELICOBACTER PYLORI UTILES POUR DES VACCINS ET DES DIAGNOSTICS.
PATENT ASSIGNEE:

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AT;BE;CH;DE;DK;ES;FR;GB;GR;IE;IT;LI;LU;MC;NL;PT;SE)
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*RAPPUOLI, Rino"**, Via Fiorentina, 1, I-53100 Siena, (IT
LEGAL REPRESENTATIVE:
Hallybone, Huw George et al (53031), CARPMAELS AND RANSFORD 43 Bloomsbury Square, London WC1A 2RA, (GB)
PATENT (CC, No, Kind, Date): EP 643770 A1 950322 (Basic)
WO 9318150 930916
APPLICATION (CC, No, Date): EP 93905285 930302; WO 93EP472 930302
PRIORITY (CC, No, Date): IT 92FI52 920302; PC EP 930125
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
RELATED DIVISIONAL NUMBER(S) - PN (AN):
(EP 99202698)
INTERNATIONAL PATENT CLASS: C12N-015/31; A61K-039/106; C12Q-001/68; G01N-033/569; C12N-015/62; A61K-037/54
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
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